UNIVERSITI PUTRA MALAYSIA

ANTI-ALLODYNIC AND ANTIHYPERALGESIC EFFECTS OF ZERUMBONE THROUGH INVOLVEMENT OF MONOAMINERGIC PATHWAYS IN MICE MODEL OF NEUROPATHIC PAIN

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FPSK(p) 2018 33

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By

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

June 2018

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

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Chairman : Enoch Kumar Perimal, PhD
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Neuropathic pain is a pain condition that arises following an injury to the nervous system, persisting past the presence of any noxious stimulus or inflammation. The complex and multifaceted mechanisms underlying the development of neuropathic pain is yet to be fully understood. For this reason, treatments available for neuropathic pain patients are not specific and do not provide sufficient pain relief. Zerumbone is the major bioactive compound found in rhizomes of the Zingiber zerumbet (L.) Smith ginger plant. Zerumbone has shown to possess multiple pharmacological potentials, most importantly in exhibiting anti-allodynic and antihyperalgesic effects in a neuropathic pain animal model. Therefore, the present study was conducted to explore the mechanisms mainly the inhibitory monoaminergic system, in the antineuropathic properties of zerumbone in a chronic constriction injury (CCI)-induced neuropathic pain mice model. The chronic constriction injury model on the sciatic nerve was employed in ICR male mice to develop neuropathic pain. The determination of the effective dosage of zerumbone in exhibiting its anti-allodynic and antihyperalgesic effects were conducted by intraperitoneal administration of zerumbone at 5, 10 and 50 mg kg on Day 14 following CCI surgery. Behavioural responses were assessed using the von Frey filament test (mechanical allodynia) and Hargreaves plantar test (thermal hyperalgesia). Zerumbone at 10 mg kg exhibited significant anti-allodynic and antihyperalgesic effects in the CCI neuropathic pain mice. The monoaminergic system is mainly controlled by serotonergic and noradrenergic projections and receptors. Investigation into the involvement of the serotonergic system was conducted by firstly depleting serotonin levels using ρ-chlorophenylalanine (PCPA), whereby zerumbone s antineuropathic properties were significantly reversed in both von Frey filament and Hargreaves plantar tests. Following this, pre-administration of specific 5-HT receptor subtype antagonists prior to zerumbone (10 mg kg) treatment significantly indicated the involvement of 5-HT

receptor subtypes 1A, 1B, 2A, 3, 6 and 7. Further investigation revealed an increase in 5-HT_{1A} receptor expression in mice brain samples following zerumbone treatment in CCI-induced neuropathic pain mice, analysed using Western Blot. Following this, the involvement of the noradrenergic system was initially investigated by administering non-specific α- and β-adrenergic receptor antagonists prior to zerumbone. Further investigation into specific adrenergic receptor subtypes revealed that mainly α_1-, α_2- and β_2-adrenergic receptors are necessary for zerumbone to exhibit its antineuropathic properties. The decrease in α_{2A}-adrenergic receptor expression suggests the inhibitory action of zerumbone against the up-regulation of these receptors following nerve injury, which has shown to facilitate nociceptive transmission. To look further into the mechanisms of action of zerumbone, prominent receptors and systems involved in the pain pathway that are known to enhance the inhibitory tone of the monoaminergic system were elucidated. The findings demonstrated the involvement of TRPV, NMDA, cannabinoid CB_1 and PPARα, PPARγ receptors in zerumbone exhibiting its anti-allodynic and antihyperalgesic effects in neuropathic pain conditions. Moreover, expression of TRPV1 and NMDA NR2B receptors increased following zerumbone treatment. Data were analysed using One-way Analysis of Variance (ANOVA) followed by Tukey's post hoc test, with the level of significance set at $p < 0.05$. In conclusion, the current study elucidated the involvement of the monoaminergic – serotonergic and noradrenergic, vanilloid, glutamatergic, cannabinoid and nuclear hormone receptor systems in zerumbone's antineuropathic properties.

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

SIFAT ANTI-ALLODINIA DAN ANTIHIPERALGESIA ZERUMBONE MENERUSI PENGLIBATAN LALUAN MONOAMINERGIK DALAM MODEL MENCIT KESAKITAN NEUROPATIK

Oleh

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Kesakitan neuropatik adalah kondisi kesakitan yang disebabkan oleh kecederaan pada sistem saraf yang berterusan melangkaui kehadiran sebarang rangsangan berbahaya atau keradangan. Mekanisme kompleks dan berbagai fungsi yang menjadi asas pembentukan kesakitan neuropatik belum lagi difahami sepenuhnya. Untuk sebab ini, rawatan sedia ada untuk pesakit neuropatik tidak khusus dan tidak memberi kelegaan kesakitan yang mencukupi. Zerumbone adalah sebatian bioaktif utama yang terdapat dalam rizom tumbuhan halia Zingiber zerumbet (L.) Smith. Zerumbone mempunyai pelbagai potensi farmakologi, terutamanya dalam menunjukkan kesan anti-allodinia dan antihiperalgesia dalam model haiwan kesakitan neuropatik. Oleh itu, kajian ini dijalankan untuk menyelidik mekanisme yang terlibat terutamanya sistem penginhibitan monoaminergik, dalam sifat antineuropatik zerumbone pada tikus neuropatik diinduksi oleh model haiwan kecederaan konstriksi kronik. Kecederaan konstriksi kronik (CCI) pada saraf siatik digunakan pada tikus jantan ICR untuk pembentukan kesakitan neuropatik. Penentuan dos berkesan zerumbone dalam mempamerkan kesan anti-allodinia dan antihiperalgesia telah dijalankan dengan suntikan intraperitoneum zerumbone pada 5, 10 dan 50 mg kg pada Hari ke-14 selepas pembedahan CCI. Tindak balas tingkah laku telah dinilai menggunakan ujian filamen von Frey (allodinia mekanikal) dan ujian plantar Hargreaves. Zerumbone pada 10 mg kg mempamerkan kesan anti-allodinia and antihiperalgesia signifikan pada tikus CCI neuropatik. Sistem monoaminergik dikawal terutamanya oleh proyeksi dan reseptor serotonergik dan noradrenergik. Siasatan ke atas penglibatan sistem serotonergik telah dilakukan dengan mengurangkan tahap serotonin menggunakan ρ-chlorophenylalanine (PCPA), dimana sifat neuropatik zerumbone dibalikkan dengan signifikan dalam kedua-dua ujian filamen von Frey dan plantar Hargreaves. Berikutan ini, pemberian antagonis subjenis reseptor 5-HT sebelum rawatan zerumbone (10 mg kg) menunjukkan penglibatan subjenis reseptor 5-HT 1A, 1B,

2A, 3, 6 dan 7 yang signifikan. Siasatan lanjut mendedahkan peningkatan dalam ekspresi reseptor 5-HT_{1A} pada sampel otak mencit berikut rawatan zerumbone dalam tikus CCI neuropatik, dianalisis dengan menggunakan Western Blot. Berikutan ini, penglibatan sistem noradrenergik pada mulanya disiasat dengan memberi antagonis tidak khusus reseptor α- dan β-adrenergik sebelum rawatan zerumbone. Siasatan lanjut pada subjenis reseptor adrenergik spesifik mendedahkan bahawa reseptor α_1-, α_2- dan β_2-adrenergik diperlukan untuk zerumbone mempamerkan sifat antineuropatiknya. Pengurangan expresi reseptor α_{2A}-adrenergik mencadangkan bahawa tindakan penginhibitan zerumbone terhadap pengawalaturan meningkat reseptor ini berikutan kecederaan saraf, yang telah ditunjukkan untuk memudahkan pengaliran nosiseptif. Untuk menyiasat dengan lebih mendalam lagi tentang mekanisme tindakan zerumbone, reseptor dan sistem yang terlibat dalam laluan kesakitan yang diketahui untuk meningkatkan nada penginhibitan sistem monoaminergik telah dijelaskan. Penemuan kajian menunjukkan penglibatan zerumbone dengan reseptor TRPV, NMDA, cannabinoid CB_1 dan PPARα, PPARγ dalam mempamerkan kesan anti-allodinik dan antihiperalgesik dalam kondisi sakit neuropatik. Tambahan lagi, ekspresi reseptor TRPV1 dan NMDA NR2B meningkat berikutan rawatan zerumbone. Data dianalisis menggunakan analisis varians (ANOVA) sehala diikuti oleh ujian post hoc Tukey, dengan tahap keertian statistik ditetapkan pada p□0.05. Kesimpulannya, kajian semasa menjelaskan penglibatan sistem monoaminergik □ serotonergik dan noradrenergik, vanilloid, glutamatergik, cannabinoid dan reseptor hormon nuklear dalam sifat antineuropatik zerumbone.

ACKNOWLEDGEMENTS

This thesis is the product of curiosity, effort, perseverance and support by those who have been with me throughout my entire postgraduate studies.

I would like to express my sincerest thanks and gratitude to my supervisor, Dr. Enoch Kumar Perimal, for his encouragements, advices and endless opportunities he has presented all through the years.

I would also like to take this opportunity to thank my co-supervisors Prof. Dr. Mohd Roslan Sulaiman and Dr. Ahmad Akira Omar Farouk for their valuable advices that have helped in accomplishing my postgraduate studies.

I am extremely thankful to my beloved family my parents for their unconditional love and support throughout my education, my sister for always standing by my side through thick and thin and my brother for his constant words of encouragement.

To my fellow lab mates in Physiology Laboratory, I am extremely grateful to have met each and every one of you. To Banulata, I am forever indebted to all the support you have given me through every step of my postgraduate journey. To Yogesvari and Ong Hui Ming, I would not have managed to come this far if not for your positivity and words of encouragement.

I am also deeply grateful to all the staffs and colleagues of the Physiology and Cell Signalling Laboratories in providing all the necessary support for this project.

I certify that a Thesis Examination Committee has met on 28 June 2018 to conduct the final examination of Jasmine Chia Siew Min on her thesis entitled "Anti-Allodynic and Antihyperalgesic Effects of Zerumbone Through Involvement of Monoaminergic Pathways in Mice Model of Neuropathic Pain" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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

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LIST OF ABBREVIATIONS

5-HT	**Serotonin**
AC	**Adenylyl Cyclase**
ACC	**Anterior Cingulate Cortex**
AMPA	**α-amino-3-hydroxy-5-methyl-4-isoxazopropionic Acid**
ANOVA	**Analysis of Variance**
AP-1	**Activator Protein-1**
AR	**Adrenergic Receptors**
ATP	**Adenosine Triphosphate**
BDNF	**Brain-derived Neurotrophic Factor**
Ca^{2+}	**Calcium Ion**
CB	**Cannabinoid**
CCI	**Chronic Constriction Injury**
CGRP	**Calcitonin Gene Related Peptide**
Cl^-	**Chloride Ion**
CNS	**Central Nervous System**
COX	**Cyclooxygenase**
DAG	**Diacyl Glycerol**
DMSO	**Dimethyl Sulfoxide**
DNIC	**Diffuse Noxious Inhibitory Control**
DRG	**Dorsal Root Ganglion**
DRN	**Dorsal Raphe Nucleus**
GABA	**γ-aminobutyric acid**
i.p.	**Intraperitoneal**
IASP	**International Association for the Study of Pain**
ICR	**Imprinting Control Region**
IL	**Interleukin**
IP_3	**Inositol Triphosphate**
K^+	**Potassium Ion**
KA	**Kainic Acid**
LC	**Locus Coeruleus**
Mg^{2+}	**Magnesium Ion**
NA	**Noradrenaline**
Na^+	**Sodium Ion**
NaCl	**Sodium Chloride (Normal Saline)**
NF-κB	**Nuclear Factor-κB**
NGF	**Nerve Growth Factor**
NMDA	**N-methyl-D-aspartate**
NO	**Nitric Oxide**
NOS	**Nitric Oxide Synthase**
PAG	**Periaqueductal Gray**
PCPA	**ρ-chlorophenylalanine**
PLC	**Phospholipase C**
PPAR	**Peroxisome Proliferator-activated Receptor**
PVDF	**Polyvinylidene Fluoride**
RVM	**Rostral Ventromedial Medulla**
SNRI	**Serotonin-Noradrenaline Reuptake Inhibitor**

STAT	**Signal Transducer and Activator of Transcription**
TBS	**Tris-buffered Saline**
TBST	**Tris-buffered Saline with Tween 20**
TCA	**Tricyclic Antidepressants**
TNF	**Tumor Necrosis Factor**
TRP	**Transient Receptor Potential**
WDR	**Wide Dynamic Range**

CHAPTER 1

INTRODUCTION

Pain is a common unpleasant sensation felt by every individual. Acute pain serves only as a warning sign to avert our body from any harmful stimuli. In contrast to acute pain, neuropathic pain persists although the harmful stimuli are no longer present. Neuropathic pain, defined as a lesion to the somatosensory nervous system, is becoming a major health issue (Dworkin, 2002). This chronic pain condition could be caused either through direct lesion, compression or injury to nerves from trauma, infections, metabolic diseases or drugs. Common diseases that are at high risk in developing neuropathic pain are diabetes, postherpetic neuralgia and multiple sclerosis (Sadosky et al., 2008; Smith and Chong, 2000).

Neuropathic pain greatly impacts a patient□s life, affecting their daily routine. The common sensations experienced are burning sensations, stabbing or shooting pain that either arises spontaneously, intermittently or only when evoked. These sensations that arises significantly affects the patient□s mood, lifestyle and activities (Deshpande et al., 2006; Gilron et al., 2006; Vinik et al., 2005). The prevalence of neuropathic pain was reported to be in the range of 1-3□ (Bouhassira et al., 2008; Bowsher, 1991; Dworkin et al., 2003; Irving, 2005). Based on reports by Cardosa et al. (2008) about 7□ of 30,000 Malaysian adults suffer from neuropathic pain. The development of this chronic pain condition is complex and does not have any singularity in its cause. As the population continues to age, the prevalence of neuropathic pain is expected to increase (Galluzzi, 2005).

In comparison to neuropathic pain, acute pain patients are treated based on the site of injury. Neuropathic pain patients on the other hand would have to go through multiple hospital visits to screen, assess and diagnose patients (Kerstman et al., 2013; Ro and Chang, 2005). Common symptoms that arise due to neuropathic pain are hyperalgesia, allodynia, paroxysms and hyperpathia (Woolf and Mannion, 1999). Medications for neuropathic pain patients are prescribed after thorough assessment of the patient□s health conditions with referment to pharmacological guidelines. The current first line of treatment is tricyclic antidepressants (Finnerup et al., 2005). Based on the pharmacological guidelines for neuropathic pain patients, a combination of medications is often prescribed to ensure efficient analgesic effects, as compared to a monotherapy strategy (Gilron et al., 2005; Gilron and Max, 2005).

Unfortunately, many neuropathic pain patients do not receive sufficient pain relief due to the challenging pathophysiology behind neuropathic pain development, inaccurate medical treatments and comorbid conditions of patients. The two main key problems with current treatments for neuropathic pain are the insufficient pain

relief and side effects that often accompany these medications (T□lle, 2010). With an estimated increase in neuropathic pain incidence worldwide due to the aging population, there is a need for a novel compound that will specifically treat neuropathic pain.

Many invaluable studies have been conducted to further explore the mechanisms behind the development of neuropathic pain and the endogenous system modulating nociceptive transmission. Multiple underlying mechanisms and pathways have been discovered (Campbell and Meyer, 2006; Perl, 2011). The monoaminergic system, which is controlled by serotonergic and noradrenergic tones, acts synergistically in inhibiting nociceptive transmission. Additionally, the inhibitory action against nociceptive transmission is a summative effect from influences of afferent pathways □ vanilloid, glutamate, cannabinoid, and nuclear hormone receptor systems (Millan, 2002).

Over the past three decades, many researches have been conducted in new drug discovery and development involving natural products (Newman and Cragg, 2012, 2016). Due to the incompatibility and high probability of causing severe side effects, synthetic compounds are often avoided. Asian countries, mainly India and China, are known to have the widest and richest array of medicinal plants (Kala et al., 2006; □uintans et al., 2014). Many now-known drugs have been either derived or are particularly similar to compounds found in natural products. In addition, natural products have been used as folkloric medicine for decades to treat various illnesses.

Ginger plants have garnered extreme attention due to its anti-inflammatory and anticancer properties, typically in South-East Asia. The rhizomes of ginger plants are known for its medicinal properties, more than its pinecone counterpart. The rhizomes have been traditionally used to treat various illnesses of inflammation and pain □ fever, constipation, stomachache (Elliott and Brimacombe, 1987; Norulaini et al., 2009; Perry and Metzger, 1980; Sulaiman et al., 2010b). Zingiber zerumbet (L.) Smith, of the Zingiber genus is a ginger plant known for its rich medicinal values. Z. zerumbet is widely distributed in Southeast Asia and the Pacific Islands (Burkill, 1966; Jantan et al., 2003; Larsen et al., 1999).

Zerumbone, the major active component of Z. zerumbet rhizomes, has been widely studied to assess its pharmacological properties (for review on previous studies, see (Yob et al., 2011)). Most importantly, zerumbone has shown prominent analgesic properties in acute and chronic pain animal models (Sulaiman et al., 2009; Zulazmi et al., 2015). Furthermore, zerumbone has displayed no toxicity at low to moderate dosages in acute toxicity studies, indicating safety of oral consumption (Ibrahim et al., 2010; Rahman et al., 2014; Sulaiman et al., 2010a).

Based on current available literatures, the opioidergic, serotonergic, cannabinoid, NMDA and TRPV systems are highly targeted by natural products to exhibit potent analgesic activity in neuropathic pain conditions (Kissin, 2010; □uintans et al., 2014). Furthermore, the underlying mechanisms behind the production of neuropathic pain and the mechanisms involved in active compounds must be clearly understood to allow synthesis of a more potent and specific treatment of targeted diseases.

Therefore, zerumbone is hypothesized to attenuate neuropathic pain symptoms □ allodynia and hyperalgesia, by acting through serotonergic, noradrenergic, vanilloid, glutamatergic, cannabinoid and peroxisome proliferator-activated systems. The findings of this study will contribute important insights to advance our knowledge on zerumbone and it□s significance in treating neuropathic pain.

Objectives of the Study

The objectives of this study are to;

1. **determine the effective dosage of zerumbone in attenuating allodynia and hyperalgesia in CCI-induced neuropathic pain mice;**
2. **investigate the involvement of serotonergic receptor subtypes and changes in 5-HT_{1A} receptor expression in the anti-allodynic and antihyperalgesic properties of zerumbone in CCI-induced neuropathic pain mice;**
3. **investigate the involvement of noradrenergic receptor subtypes and changes in α_{2A}-adrenergic receptor expression in the anti-allodynic and antihyperalgesic properties of zerumbone in CCI-induced neuropathic pain mice;**
4. **investigate the involvement of TRPV and NMDA receptors and changes in TRPV VR1 and NMDA NR2B receptors expression in the anti-allodynic and antihyperalgesic properties of zerumbone in CCI-induced neuropathic pain mice;**
5. **investigate the involvement of cannabinoid receptors in the anti-allodynic and antihyperalgesic properties of zerumbone in CCI-induced neuropathic pain mice;**
6. **investigate the involvement of peroxisome proliferator-activated receptors in the anti-allodynic and antihyperalgesic properties of zerumbone in CCI-induced neuropathic pain mice.**

REFERENCES

Aantaa, R., Marjamaki, A., □ Scheinin, M. (1995). Molecular pharmacology of alpha 2-adrenoceptor subtypes. Annals of Medicine, 27(4), 439-449.

Abel, E. L. (2013). Marihuana: The first twelve thousand years: Springer Science □ Business Media.

Acher, F., □ Goudet, C. (2015). Therapeutic potential of group III metabotropic glutamate receptor ligands in pain. Current Opinion in Pharmacology, 20, 64-72.

Ahern, G. P., Brooks, I. M., Miyares, R. L., □ Wang, X.-b. (2005). Extracellular cations sensitize and gate capsaicin receptor TRPV1 modulating pain signaling. Journal of Neuroscience, 25(21), 5109-5116.

Ahern, G. P., Wang, X., □ Miyares, R. L. (2006). Polyamines are potent ligands for the capsaicin receptor TRPV1. Journal of Biological Chemistry, 281(13), 8991-8995.

Aira, Z., Buesa, I., Garcia del Cano, G., Salgueiro, M., Mendiable, N., Mingo, J., Aguilera, L., Bilbao, J., □ Azkue, J. J. (2012). Selective impairment of spinal mu-opioid receptor mechanism by plasticity of serotonergic facilitation mediated by 5-HT2a and 5-HT2b receptors. Pain, 153(7), 1418-1425.

Aira, Z., Buesa, I., Salgueiro, M., Bilbao, J., Aguilera, L., Zimmermann, M., □ Azkue, J. J. (2010). Subtype-specific changes in 5-HT receptor-mediated modulation of c fibre-evoked spinal field potentials are triggered by peripheral nerve injury. Neuroscience, 168(3), 831-841.

al-Ghoul, W. M., Li Volsi, G., Weinberg, R. J., □ Rustioni, A. (1993). Glutamate immunocytochemistry in the dorsal horn after injury or stimulation of the sciatic nerve of rats. Brain Research Bulletin, 30(3-4), 453-459.

Alba-Delgado, C., Llorca-Torralba, M., Horrillo, I., Ortega, J. E., Mico, J. A., S□nchez-Bl□zquez, P., Meana, J. J., □ Berrocoso, E. (2013). Chronic pain leads to concomitant noradrenergic impairment and mood disorders. Biological Psychiatry, 73(1), 54-62.

Alba-Delgado, C., Mico, J. A., Sanchez-Blazquez, P., □ Berrocoso, E. (2012). Analgesic antidepressants promote the responsiveness of locus coeruleus neurons to noxious stimulation: Implications for neuropathic pain. Pain, 153(7), 1438-1449.

Albert, P. R., Le Francois, B., □ Millar, A. M. (2011). Transcriptional dysregulation of 5-HT1a autoreceptors in mental illness. Molecular Brain Research, 4, 21.

Alexander, S. P., Mathie, A., □ Peters, J. A. (2008). Guide to receptors and channels (GRAC), 3rd edition. British Journal of Pharmacology, 153 Suppl 2, S1-209.

Alhaider, A. A., Lei, S. Z., □ Wilcox, G. L. (1991). Spinal 5-HT3 receptor-mediated antinociception: Possible release of GABA. Journal of Neuroscience, 11(7), 1881-1888.

Ali, Z., Raja, S. N., Wesselmann, U., Fuchs, P. N., Meyer, R. A., □ Campbell, J. N. (2000). Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. Pain, 88(2), 161-168.

Ali, Z., Ringkamp, M., Hartke, T. V., Chien, H. F., Flavahan, N. A., Campbell, J. N., □ Meyer, R. A. (1999). Uninjured c-fiber nociceptors develop spontaneous activity and α-adrenergic sensitivity following L6 spinal nerve ligation in monkey. Journal of Neurophysiology, 81(2), 455-466.

Allen, A. R. (1911). Surgery of experimental lesion of spinal cord equivalent to crush injury of fracture dislocation of spinal column: A preliminary report. Journal of the American Medical Association, 57(11), 878-880.

Almeida, T. F., Roizenblatt, S., □ Tufik, S. (2004). Afferent pain pathways: A neuroanatomical review. Brain Research, 1000(1-2), 40-56.

Amir, R., Argoff, C. E., Bennett, G. J., Cummins, T. R., Durieux, M. E., Gerner, P., Gold, M. S., Porreca, F., □ Strichartz, G. R. (2006). The role of sodium channels in chronic inflammatory and neuropathic pain. The Journal of Pain, 7(5), S1-S29.

Anand, P., □ Bley, K. (2011). Topical capsaicin for pain management: Therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8□ patch. British Journal of Anaesthesia, 107(4), 490-502.

Arch, J. R. (2002). Beta(3)-adrenoceptor agonists: Potential, pitfalls and progress. European Journal of Pharmacology, 440(2-3), 99-107.

Ardid, D., Alloui, A., Brousse, G., Jourdan, D., Picard, P., Dubray, C., □ Eschalier, A. (2001). Potentiation of the antinociceptive effect of clomipramine by a 5-HT(1a) antagonist in neuropathic pain in rats. British Journal of Pharmacology, 132(5), 1118-1126.

Asano, T., Dohi, S., □ Iida, H. (2000a). Antinociceptive action of epidural K□ ATP channel openers via interaction with morphine and an α2-adrenergic agonist in rats. Anesthesia □ Analgesia, 90(5), 1146-1151.

Asano, T., Dohi, S., Ohta, S., Shimonaka, H., Iida, H. (2000b). Antinociception by epidural and systemic α2-adrenoceptor agonists and their binding affinity in rat spinal cord and brain. Anesthesia Analgesia, 90(2), 400-407.

Attal, N., Cruccu, G., Baron, R., Haanpaa, M., Hansson, P., Jensen, T. S., Nurmikko, T., European Federation of Neurological, S. (2010). EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. European Journal of Neurology, 17(9), 1113-e1188.

Attal, N., Cruccu, G., Haanpaa, M., Hansson, P., Jensen, T. S., Nurmikko, T., Sampaio, C., Sindrup, S., Wiffen, P., Force, E. T. (2006). EFNS guidelines on pharmacological treatment of neuropathic pain. European Journal of Neurology, 13(11), 1153-1169.

Bailey, A. L., Ribeiro-da-Silva, A. (2006). Transient loss of terminals from non-peptidergic nociceptive fibers in the substantia gelatinosa of spinal cord following chronic constriction injury of the sciatic nerve. Neuroscience, 138(2), 675-690.

Bajic, D., Proudfit, H. K. (1999). Projections of neurons in the periaqueductal gray to pontine and medullary catecholamine cell groups involved in the modulation of nociception. Journal of Comparative Neurology, 405(3), 359-379.

Ballantyne, J. C., LaForge, S. K. (2007). Opioid dependence and addiction during opioid treatment of chronic pain. Pain, 129(3), 235-255.

Bambico, F. R., Katz, N., Debonnel, G., Gobbi, G. (2007). Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex. Journal of Neuroscience, 27(43), 11700-11711.

Baptista-de-Souza, D., Mannelli, L. D. C., Zanardelli, M., Micheli, L., Nunes-de-Souza, R. L., Canto-de-Souza, A., Ghelardini, C. (2014). Serotonergic modulation in neuropathy induced by oxaliplatin: Effect on the 5HT 2c receptor. European Journal of Pharmacology, 735, 141-149.

Bardin, L. (2011). The complex role of serotonin and 5-HT receptors in chronic pain. Behavioural Pharmacology, 22(5 and 6), 390-404.

Bardin, L., Lavarenne, J., Eschalier, A. (2000). Serotonin receptor subtypes involved in the spinal antinociceptive effect of 5-HT in rats. Pain, 86(1), 11-18.

Barnes, N. M., Sharp, T. (1999). A review of central 5-HT receptors and their function. Neuropharmacology, 38(8), 1083-1152.

Baron, R. (2006). Mechanisms of disease: Neuropathic pain--a clinical perspective. Nature Reviews Neurology, 2(2), 95-106.

Baron, R., Binder, A., Wasner, G. (2010). Neuropathic pain: Diagnosis, pathophysiological mechanisms, and treatment. The Lancet Neurology, 9(8), 807-819.

Barrot, M., Yalcin, I., Choucair-Jaafar, N., Benbouzid, M., Freund-Mercier, M. J. (2009). From antidepressant drugs to beta-mimetics: Preclinical insights on potential new treatments for neuropathic pain. Recent Patents on CNS Drug Discovery, 4(3), 182-189.

Basbaum, A. I., Bautista, D. M., Scherrer, G., Julius, D. (2009). Cellular and molecular mechanisms of pain. Cell, 139(2), 267-284.

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

Basbaum, A. I., Jessell, T. M. (2000). The perception of pain. Principles of Neural Science, 4, 472-491.

Becker, N., Thomsen, A. B., Olsen, A. K., Sjgren, P., Bech, P., Eriksen, J. (1997). Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. Pain, 73(3), 393-400.

Beecher, H. K. (1946). Pain in men wounded in battle. The Bulletin of the US Army Medical Department, 5, 445-454.

Bektas, N., Arslan, R., Ozturk, Y. (2014). Zonisamide: Antihyperalgesic efficacy, the role of serotonergic receptors on efficacy in a rat model for painful diabetic neuropathy. Life Sciences, 95(1), 9-13.

Belcher, G., Ryall, R., Schaffner, R. (1978). The differential effects of 5-hydroxytryptamine, noradrenaline and raphe stimulation on nociceptive and non-nociceptive dorsal horn interneurones in the cat. Brain Research, 151(2), 307-321.

Benarroch, E. E. (2012). Endogenous opioid systems: Current concepts and clinical correlations. Neurology, 79(8), 807-814.

Benbouzid, M., Choucair-Jaafar, N., Yalcin, I., Waltisperger, E., Muller, A., Freund-Mercier, M. J., Barrot, M. (2008). Chronic, but not acute, tricyclic antidepressant treatment alleviates neuropathic allodynia after sciatic nerve cuffing in mice. European Journal of Pain, 12(8), 1008-1017.

Bennett, G. J. (2000). Update on the neurophysiology of pain transmission and modulation: Focus on the NMDA-receptor. Journal of Pain and Symptom Management, 19(1 Suppl), S2-6.

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(1), 87-107.

Berger, M., Gray, J. A., □ Roth, B. L. (2009). The expanded biology of serotonin. Annual Review of Medicine, 60, 355-366.

Berghe, W. V., Vermeulen, L., Delerive, P., De Bosscher, K., Staels, B., □ Haegeman, G. (2003). A paradigm for gene regulation: Inflammation, NF-κb and PPAR Peroxisomal disorders and regulation of genes (pp. 181-196): Springer.

Berrocoso, E., Mico, J. A., Vitton, O., Ladure, P., Newman-Tancredi, A., Depoortere, R., □ Bardin, L. (2011). Evaluation of milnacipran, in comparison with amitriptyline, on cold and mechanical allodynia in a rat model of neuropathic pain. European Journal of Pharmacology, 655(1-3), 46-51.

Besson, J. M., □ Chaouch, A. (1987). Peripheral and spinal mechanisms of nociception. Physiological Reviews, 67(1), 67-186.

Bingel, U., □ Tracey, I. (2008). Imaging CNS modulation of pain in humans. Physiology, 23(6), 371-380.

Bingham, B., Ajit, S. K., Blake, D. R., □ Samad, T. A. (2009). The molecular basis of pain and its clinical implications in rheumatology. Nature Reviews Rheumatology, 5(1), 28-37.

Bleakman, D., Alt, A., □ Nisenbaum, E. S. (2006). Glutamate receptors and pain. Seminars in Cell and Developmental Biology, 17(5), 592-604.

Bodor, □. L., Katona, I., Ny□ri, G., Mackie, K., Ledent, C., H□jos, N., □ Freund, T. F. (2005). Endocannabinoid signaling in rat somatosensory cortex: Laminar differences and involvement of specific interneuron types. Journal of Neuroscience, 25(29), 6845-6856.

Borchardt, J. K. (2002). The beginnings of drug therapy: Ancient mesopotamian medicine. Drug News □ Perspectives, 15(3), 187-192.

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(3), 380-387.

Bourgoin, S., Viguier, F., Michot, B., Kayser, V., Vela, J., Hamon, M. (2008). 5-HT receptor stimulation exerts anti-hyperalgesic effects in rats suffering from neuropathic pain via activation of GABAergic interneurons. Fundamental Clinical Pharmacology, 22, 127-128.

Bowsher, D. (1991). Neurogenic pain syndromes and their management. British Medical Bulletin, 47(3), 644-666.

Brenchat, A., Nadal, X., Romero, L., Ovalle, S., Muro, A., Sanchez-Arroyos, R., Portillo-Salido, E., Pujol, M., Montero, A., Codony, X., Burgueno, J., Zamanillo, D., Hamon, M., Maldonado, R., Vela, J. M. (2010). Pharmacological activation of 5-HT7 receptors reduces nerve injury-induced mechanical and thermal hypersensitivity. Pain, 149(3), 483-494.

Brenchat, A., Romero, L., Garcia, M., Pujol, M., Burgueno, J., Torrens, A., Hamon, M., Baeyens, J. M., Buschmann, H., Zamanillo, D., Vela, J. M. (2009). 5-HT7 receptor activation inhibits mechanical hypersensitivity secondary to capsaicin sensitization in mice. Pain, 141(3), 239-247.

Brenchat, A., Zamanillo, D., Hamon, M., Romero, L., Vela, J. M. (2012). Role of peripheral versus spinal 5-HT(7) receptors in the modulation of pain undersensitizing conditions. European Journal of Pain, 16(1), 72-81.

Brenneisen, R. (2007). Chemistry and analysis of phytocannabinoids and other cannabis constituents. Marijuana and the Cannabinoids, 17-49.

Brightwell, J. J., Taylor, B. K. (2009). Noradrenergic neurons in the locus coeruleus contribute to neuropathic pain. Neuroscience, 160(1), 174-185.

Bristow, M. R., Ginsburg, R., Umans, V., Fowler, M., Minobe, W., Rasmussen, R., Zera, P., Menlove, R., Shah, P., Jamieson, S., et al. (1986). Beta 1- and beta 2-adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: Coupling of both receptor subtypes to muscle contraction and selective beta 1-receptor down-regulation in heart failure. Circulation Research, 59(3), 297-309.

Brodde, O. E., Michel, M. C. (1999). Adrenergic and muscarinic receptors in the human heart. Pharmacological Reviews, 51(4), 651-690.

Budai, D., Fields, H. L. (1998). Endogenous opioid peptides acting at mu-opioid receptors in the dorsal horn contribute to midbrain modulation of spinal nociceptive neurons. Journal of Neurophysiology, 79(2), 677-687.

Budai, D., Harasawa, I., Fields, H. L. (1998). Midbrain periaqueductal gray (PAG) inhibits nociceptive inputs to sacral dorsal horn nociceptive neurons through α2-adrenergic receptors. Journal of Neurophysiology, 80(5), 2244-2254.

Bujalska, M. (2008). Effect of cannabinoid receptor agonists on streptozotocin-induced hyperalgesia in diabetic neuropathy. Pharmacology, 82(3), 193-200.

Burkill, I. H. (1966). A dictionary of the economic products of the malay peninsula (Vol. 2).

Butler, M. S. (2008). Natural products to drugs: Natural product-derived compounds in clinical trials. Natural Product Reports, 25(3), 475-516.

Bylund, D. B. (1995). Pharmacological characteristics of alpha-2 adrenergic receptor subtypes. Annals of the New York Academy of Sciences, 763, 1-7.

Bylund, D. B., Eikenberg, D. C., Hieble, J. P., Langer, S. Z., Lefkowitz, R. J., Minneman, K. P., Molinoff, P. B., Ruffolo, R. R., Jr., □ Trendelenburg, U. (1994). International union of pharmacology nomenclature of adrenoceptors. Pharmacological Reviews, 46(2), 121-136.

Calixto, J. B., Beirith, A., Ferreira, J., Santos, A. R., □ Yunes, R. A. (2000). Naturally occurring antinociceptive substances from plants. Phytotherapy Research, 14(6), 401-418.

Calixto, J. B., Santos, A. R., Filho, V. C., □ Yunes, R. A. (1998). A review of the plants of the genus phyllanthus: Their chemistry, pharmacology, and therapeutic potential. Medicinal Research Reviews, 18(4), 225-258.

Calvo, M., Dawes, J. M., □ Bennett, D. L. (2012). The role of the immune system in the generation of neuropathic pain. The Lancet Neurology, 11(7), 629-642.

Campbell, J. N., □ Meyer, R. A. (2006). Mechanisms of neuropathic pain. Neuron, 52(1), 77-92.

Cardosa, M., Gurpreet, R., □ Tee, H. (2008). Chronic pain, the third national health and morbidity survey 2006, vol. 1. Kuala Lumpur: Institute for Public Health, Ministry of Health Malaysia, 262.

Carlton, S. M., Dougherty, P. M., Pover, C. M., □ Coggeshall, R. E. (1991). Neuroma formation and numbers of axons in a rat model of experimental peripheral neuropathy. Neuroscience Letters, 131(1), 88-92.

Castaneda-Corral, G., Rocha-Gonzalez, H. I., Araiza-Saldana, C. I., Ambriz-Tututi, M., Vidal-Cantu, G. C., □ Granados-Soto, V. (2009). Role of peripheral and spinal 5-HT6 receptors according to the rat formalin test. Neuroscience, 162(2), 444-452.

Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D., & Julius, D. (1997). The capsaicin receptor: A heat-activated ion channel in the pain pathway. Nature, 389(6653), 816-824.

Cathryn R, H., Lee, T., & N Bradley, K. (2012). 5-HT 2a receptor activation normalizes exaggerated fear behavior in p-chlorophenylalanine (PCPA)-treated rats. Journal of Behavioral and Brain Science, 2012.

Caulfield, M. P., & Brown, D. A. (1992). Cannabinoid receptor agonists inhibit ca current in ng108-15 neuroblastoma cells via a pertussis toxin-sensitive mechanism. British Journal of Pharmacology, 106(2), 231-232.

Cavanaugh, D. J., Lee, H., Lo, L., Shields, S. D., Zylka, M. J., Basbaum, A. I., & Anderson, D. J. (2009). Distinct subsets of unmyelinated primary sensory fibers mediate behavioral responses to noxious thermal and mechanical stimuli. Proceedings of the National Academy of Sciences, 106(22), 9075-9080.

Cervantes-Duran, C., Rocha-Gonzalez, H. I., & Granados-Soto, V. (2013). Peripheral and spinal 5-HT receptors participate in the pronociceptive and antinociceptive effects of fluoxetine in rats. Neuroscience, 252, 396-409.

Chakraborty, S., Elvezio, V., Kaczocha, M., Rebecchi, M., & Puopolo, M. (2017). Presynaptic inhibition of transient receptor potential vanilloid type 1 (TRPV1) receptors by noradrenaline in nociceptive neurons. The Journal of Physiology, 595(8), 2639-2660.

Challa, S. R. (2015). Surgical animal models of neuropathic pain: Pros and cons. International Journal of Neuroscience, 125(3), 170-174.

Chaplan, S. R., Bach, F. W., Pogrel, J. W., Chung, J. M., & Yaksh, T. L. (1994). uantitative assessment of tactile allodynia in the rat paw. Journal of Neuroscience Methods, 53(1), 55-63.

Chaplan, S. R., Malmberg, A. B., & Yaksh, T. L. (1997). Efficacy of spinal NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. Journal of Pharmacology and Experimental Therapeutics, 280(2), 829-838.

Chapman, C. R., Tuckett, R. P., & Song, C. W. (2008). Pain and stress in a systems perspective: Reciprocal neural, endocrine, and immune interactions. The Journal of Pain, 9(2), 122-145.

Charney, D. S., Heninger, G. R., & Sternberg, D. E. (1984). Serotonin function and mechanism of action of antidepressant treatment: Effects of amitriptyline and desipramine. Archives of General Psychiatry, 41(4), 359-365.

Chen, Y., Oatway, M. A., □ Weaver, L. C. (2009). Blockade of the 5-HT3 receptor for days causes sustained relief from mechanical allodynia following spinal cord injury. Journal of Neuroscience Research, 87(2), 418-424.

Chen, Y. W., Li, Y. T., Chen, Y. C., Li, Z. Y., □ Hung, C. H. (2012). Exercise training attenuates neuropathic pain and cytokine expression after chronic constriction injury of rat sciatic nerve. Anesthesia □ Analgesia, 114(6), 1330-1337.

Chenaf, C., Chapuy, E., Libert, F., Marchand, F., Courteix, C., Bertrand, M., Gabriel, C., Mocaer, E., Eschalier, A., □ Authier, N. (2017). Agomelatine: A new opportunity to reduce neuropathic pain-preclinical evidence. Pain, 158(1), 149-160.

Chien, T. Y., Huang, S. K., 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(2), 249.

Chilmonczyk, Z., Bojarski, A. J., Pilc, A., □ Sylte, I. (2015). Functional selectivity and antidepressant activity of serotonin 1a receptor ligands. International Journal of Molecular Sciences, 16(8), 18474-18506.

Chojnacka-W□jcik, E., Kłodzińska, A., □ Deręń-Wesołek, A. (1994). Involvement of 5-HT2c receptors in the m-cpp-induced antinociception in mice. Polish Journal of Pharmacology, 46(5), 423-428.

Choucair-Jaafar, N., Yalcin, I., Rodeau, J. L., Waltisperger, E., Freund-Mercier, M. J., □ Barrot, M. (2009). Beta2-adrenoceptor agonists alleviate neuropathic allodynia in mice after chronic treatment. British Journal of Pharmacology, 158(7), 1683-1694.

Churi, S. B., Abdel-Aleem, O. S., Tumber, K. K., Scuderi-Porter, H., □ Taylor, B. K. (2008). Intrathecal rosiglitazone acts at peroxisome proliferator□ activated receptor-γ to rapidly inhibit neuropathic pain in rats. The Journal of Pain, 9(7), 639-649.

Collingridge, G. L., Volianskis, A., Bannister, N., France, G., Hanna, L., Mercier, M., Tidball, P., Fang, G., Irvine, M. W., Costa, B. M., Monaghan, D. T., Bortolotto, Z. A., Molnar, E., Lodge, D., □ Jane, D. E. (2013). The NMDA receptor as a target for cognitive enhancement. Neuropharmacology, 64, 13-26.

Connor, M., □ Christie, M. D. (1999). Opioid receptor signalling mechanisms. Clinical and Experimental Pharmacology and Physiology, 26(7), 493-499.

Cooper, J. R., Bloom, F. E., Roth, R. H. (2003). The biochemical basis of neuropharmacology: Oxford University Press, USA.

Costa, B., Colleoni, M., Conti, S., Trovato, A. E., Bianchi, M., Sotgiu, M. L., Giagnoni, G. (2004). Repeated treatment with the synthetic cannabinoid win 55,212-2 reduces both hyperalgesia and production of pronociceptive mediators in a rat model of neuropathic pain. British Journal of Pharmacology, 141(1), 4-8.

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 CB(1), TRPV1 and PPARgamma receptors and neurotrophic factors. Pain, 139(3), 541-550.

Coull, J. A., Beggs, S., Boudreau, D., Boivin, D., Tsuda, M., Inoue, K., Gravel, C., Salter, M. W., De Koninck, Y. (2005). BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. Nature, 438(7070), 1017-1021.

Coull, J. A., Boudreau, D., Bachand, K., Prescott, S. A., Nault, F., Sik, A., De Koninck, P., De Koninck, Y. (2003). Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain. Nature, 424(6951), 938-942.

Cragg, G. M., Kingston, D. G., Newman, D. J. (2011). Anticancer agents from natural products: CRC press.

Crisp, T., Stafinsky, J. L., Spanos, L. J., Uram, M., Perni, V. C., Donepudi, H. B. (1991). Analgesic effects of serotonin and receptor-selective serotonin agonists in the rat spinal cord. General Pharmacology: The Vascular System, 22(2), 247-251.

Cross, S. A. (1994). Pathophysiology of pain. Paper presented at the Mayo Clinic Proceedings.

Croxford, J. L., Yamamura, T. (2005). Cannabinoids and the immune system: Potential for the treatment of inflammatory diseases Journal of Neuroimmunology, 166(1), 3-18.

Cui, M., Feng, Y., McAdoo, D., Willis, W. (1999). Periaqueductal gray stimulation-induced inhibition of nociceptive dorsal horn neurons in rats is associated with the release of norepinephrine, serotonin, and amino acids. Journal of Pharmacology and Experimental Therapeutics, 289(2), 868-876.

D Mello, R., Dickenson, A. H. (2008). Spinal cord mechanisms of pain. British Journal of Anaesthesia, 101(1), 8-16.

Da Silva, L. F., DeSantana, J. M., □ Sluka, K. A. (2010). Activation of NMDA receptors in the brainstem, rostral ventromedial medulla, and nucleus reticularis gigantocellularis mediates mechanical hyperalgesia produced by repeated intramuscular injections of acidic saline in rats. The Journal of Pain, 11(4), 378-387.

Davis, J. B., Gray, J., Gunthorpe, M. J., Hatcher, J. P., Davey, P. T., Overend, P., Harries, M. H., Latcham, J., Clapham, C., □ Atkinson, K. (2000). Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. Nature, 405(6783), 183-187.

Day, H. E., Campeau, S., Watson, S. J., Jr., □ Akil, H. (1997). Distribution of alpha 1a-, alpha 1b- and alpha 1d-adrenergic receptor mrna in the rat brain and spinal cord. Journal of Chemical Neuroanatomy, 13(2), 115-139.

Daynes, R. A., □ Jones, D. C. (2002). Emerging roles of PPARs in inflammation and immunity. Nature Reviews Immunology, 2(10), 748-759.

De Montigny, C., Blier, P., □ Chaput, Y. (1984). Electrophysiologically-identified serotonin receptors in the rat cns: Effect of antidepressant treatment. Neuropharmacology, 23(12), 1511-1520.

De Vry, J., Kuhl, E., Franken-Kunkel, P., □ Eckel, G. (2004). Pharmacological characterization of the chronic constriction injury model of neuropathic pain. European Journal of Pharmacology, 491(2-3), 137-148.

Deshpande, M. A., Holden, R. R., □ Gilron, I. (2006). The impact of therapy on quality of life and mood in neuropathic pain: What is the effect of pain reduction□Anesthesia □ Analgesia, 102(5), 1473-1479.

Deumens, R., Bozkurt, A., Meek, M. F., Marcus, M. A., Joosten, E. A., Weis, J., □ Brook, G. A. (2010). Repairing injured peripheral nerves: Bridging the gap. Progress in Neurobiology, 92(3), 245-276.

Dev, S. (1960). Studies in sesquiterpenes□ xvi. Tetrahedron, 8(3), 171-180.

Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., □ Mechoulam, R. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science, 258(5090), 1946-1949.

Devchand, P. R., Keller, H., Peters, J. M., Vazquez, M., Gonzalez, F. J., □ Wahli, W. (1996). The PPARalpha-leukotriene B4 pathway to inflammation control. Nature, 384(6604), 39-43.

Di Cesare Mannelli, L., D□Agostino, G., Pacini, A., Russo, R., Zanardelli, M., Ghelardini, C., □ Calignano, A. (2013). Palmitoylethanolamide is a disease-modifying agent in peripheral neuropathy: Pain relief and

neuroprotection share a PPAR-alpha-mediated mechanism. Mediators of Inflammation, 2013.

Dmitrieva, N., Rodriguez-Malaver, A. J., Perez, J., Hernandez, L. (2004). Differential release of neurotransmitters from superficial and deep layers of the dorsal horn in response to acute noxious stimulation and inflammation of the rat paw. European Journal of Pain, 8(3), 245-252.

Doğrul, A., Gül, H., Yildiz, O., Bilgin, F., Gözeldemir, M. E. (2004). Cannabinoids blocks tactile allodynia in diabetic mice without attenuation of its antinociceptive effect. Neuroscience Letters, 368(1), 82-86.

Dogrul, A., Ossipov, M. H., Porreca, F. (2009). Differential mediation of descending pain facilitation and inhibition by spinal 5HT-3 and 5HT-7 receptors. Brain Research, 1280, 52-59.

Dogrul, A., Seyrek, M., Yalcin, B., Ulugol, A. (2012). Involvement of descending serotonergic and noradrenergic pathways in cb1 receptor-mediated antinociception. Progress in Neuropsychopharmacology Biological Psychiatry, 38(1), 97-105.

Donvito, G., Bagdas, D., Toma, W., Rahimpour, E., Jackson, A., Meade, J. A., AlSharari, S., Kulkarni, A. R., Carroll, F. I., Lichtman, A. H. (2017). The interaction between alpha 7 nicotinic acetylcholine receptor and nuclear peroxisome proliferator-activated receptor-α represents a new antinociceptive signaling pathway in mice. Experimental Neurology, 295, 194-201.

Dubin, A. E., Patapoutian, A. (2010). Nociceptors: The sensors of the pain pathway. Journal of Clinical Investigation, 120(11), 3760-3772.

Dubový, P. (2011). Wallerian degeneration and peripheral nerve conditions for both axonal regeneration and neuropathic pain induction. Annals of Anatomy-Anatomischer Anzeiger, 193(4), 267-275.

Dworkin, R. H. (2002). An overview of neuropathic pain: Syndromes, symptoms, signs, and several mechanisms. The Clinical Journal of Pain, 18(6), 343-349.

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., Hewitt, D. J., Loeser, J. D., Max, M. B., Saltarelli, M., Schmader, K. E., Stein, C., Thompson, D., Turk, D. C., Wallace, M. S., Watkins, L. R., Weinstein, S. M. (2003). Advances in neuropathic pain: Diagnosis, mechanisms, and treatment recommendations. Archives of Neurology, 60(11), 1524-1534.

Eide, P. K., □ Hole, K. (1991). Different role of 5-HT1a and 5-HT2 receptors in spinal cord in the control of nociceptive responsiveness. Neuropharmacology, 30(7), 727-731.

Eide, P. K., Jorum, E., Stubhaug, A., Bremnes, J., □ Breivik, H. (1994). Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: A double-blind, cross-over comparison with morphine and placebo. Pain, 58(3), 347-354.

Eippert, F., Finsterbusch, J., Bingel, U., □ B□chel, C. (2009). Direct evidence for spinal cord involvement in placebo analgesia. Science, 326(5951), 404-404.

Eisenach, J. C., De Kock, M., □ Klimscha, W. (1996). A2-adrenergic agonists for regional anesthesiaa clinical review of clonidine (1984-1995). The Journal of the American Society of Anesthesiologists, 85(3), 655-674.

Eisenach, J. C., Hood, D. D., □ Curry, R. (1998). Intrathecal, but not intravenous, clonidine reduces experimental thermal or capsaicin-induced pain and hyperalgesia in normal volunteers. Anesthesia □ Analgesia, 87(3), 591-596.

Eisenberg, E., LaCross, S., □ Strassman, A. M. (1995). The clinically tested n-methyl-d-aspartate receptor antagonist memantine blocks and reverses thermal hyperalgesia in a rat model of painful mononeuropathy. Neuroscience Letters, 187(1), 17-20.

Elliott, S., □ Brimacombe, J. (1987). The medicinal plants of Gunung Leuser national park, Indonesia. Journal of Ethnopharmacology, 19(3), 285-317.

Ellis, A., □ Bennett, D. (2013). Neuroinflammation and the generation of neuropathic pain. British Journal of Anaesthesia, 111(1), 26-37.

Epstein, J. B., □ Marcoe, J. H. (1994). Topical application of capsaicin for treatment of oral neuropathic pain and trigeminal neuralgia. Oral Surgery, Oral Medicine, Oral Pathology, 77(2), 135-140.

Escher, P., □ Wahli, W. (2000). Peroxisome proliferator-activated receptors: Insight into multiple cellular functions. Mutation Research, 448(2), 121-138.

Evans, R. M., Barish, G. D., □ Wang, Y. X. (2004). PPARs and the complex journey to obesity. Nature Medicine, 10(4), 355-361.

Faber, E. L., □ Sah, P. (2003). Calcium-activated potassium channels: Multiple contributions to neuronal function. The Neuroscientist, 9(3), 181-194.

Fabricant, D. S., Farnsworth, N. R. (2001). The value of plants used in traditional medicine for drug discovery. Environmental Health Perspectives, 109(Suppl 1), 69.

Fajas, L., Auboeuf, D., Raspe, E., Schoonjans, K., Lefebvre, A. M., Saladin, R., Najib, J., Laville, M., Fruchart, J. C., Deeb, S., Vidal-Puig, A., Flier, J., Briggs, M. R., Staels, B., Vidal, H., Auwerx, J. (1997). The organization, promoter analysis, and expression of the human PPARgamma gene. Journal of Biological Chemistry, 272(30), 18779-18789.

Felder, C. C., Joyce, K. E., Briley, E. M., Mansouri, J., Mackie, K., Blond, O., Lai, Y., Ma, A. L., Mitchell, R. L. (1995). Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. Molecular Pharmacology, 48(3), 443-450.

Felsby, S., Nielsen, J., Arendt-Nielsen, L., Jensen, T. S. (1996). NMDA receptor blockade in chronic neuropathic pain: A comparison of ketamine and magnesium chloride. Pain, 64(2), 283-291.

Feng, X., Zhang, F., Dong, R., Li, W., Liu, J., Zhao, X., Xue, ., Yu, B., Xu, J. (2009). Intrathecal administration of clonidine attenuates spinal neuroimmune activation in a rat model of neuropathic pain with existing hyperalgesia. European Journal of Pharmacology, 614(1-3), 38-43.

Fields, H. L., Heinricher, M. M., Mason, P. (1991). Neurotransmitters in nociceptive modulatory circuits. Annual Review of Neuroscience, 14, 219-245.

Fine, P., Ashburn, M. (1998). Functional neuroanatomy and nociception. The Management of Pain, 1-16.

Fine, P. G., Rosenfeld, M. J. (2014). Cannabinoids for neuropathic pain. Current Pain and Headache Reports, 18(10), 451.

Finnerup, N. B., Otto, M., Mcuay, H. J., Jensen, T. S., Sindrup, S. H. (2005). Algorithm for neuropathic pain treatment: An evidence based proposal. Pain, 118(3), 289-305.

Finnerup, N. B., Sindrup, S. H., Jensen, T. S. (2007). Chronic neuropathic pain: Mechanisms, drug targets and measurement. Fundamental Clinical Pharmacology, 21(2), 129-136.

Fleetwood-Walker, S. M., Mitchell, R., Hope, P. J., Molony, V., Iggo, A. (1985). An α 2 receptor mediates the selective inhibition by noradrenaline of nociceptive responses of identified dorsal horn neurones. Brain Research, 334(2), 243-254.

Freitag, C. M., □ Miller, R. J. (2014). Peroxisome proliferator-activated receptor agonists modulate neuropathic pain: A link to chemokines□Frontiers in Cellular Neuroscience, 8, 238.

Frostick, S. P., Yin, □., □ Kemp, G. J. (1998). Schwann cells, neurotrophic factors, and peripheral nerve regeneration. Microsurgery, 18(7), 397-405.

Fukuoka, T., Tokunaga, A., Tachibana, T., Dai, Y., Yamanaka, H., □ Noguchi, K. (2002). VR1, but not P2X 3, increases in the spared L4 DRG in rats with L5 spinal nerve ligation. Pain, 99(1), 111-120.

Fundytus, M. E. (2001). Glutamate receptors and nociception: Implications for the drug treatment of pain. CNS Drugs, 15(1), 29-58.

Gabay, E., □ Tal, M. (2004). Pain behavior and nerve electrophysiology in the CCI model of neuropathic pain. Pain, 110(1-2), 354-360.

Galiegue, S., Mary, S., Marchand, J., Dussossoy, D., Carriere, D., Carayon, P., Bouaboula, M., Shire, D., Le Fur, G., □ Casellas, P. (1995). Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. European Journal of Biochemistry, 232(1), 54-61.

Galluzzi, K. E. (2005). Management of neuropathic pain. The Journal of the American Osteopathic Association, 105(suppl_4), S12-S19.

Gao, K., Kim, Y. H., □ Mason, P. (1997). Serotonergic pontomedullary neurons are not activated by antinociceptive stimulation in the periaqueductal gray. Journal of Neuroscience, 17(9), 3285-3292.

Garcia-Garcia, A. L., Newman-Tancredi, A., □ Leonardo, E. D. (2014). 5-HT(1a) □corrected□ receptors in mood and anxiety: Recent insights into autoreceptor versus heteroreceptor function. Psychopharmacology, 231(4), 623-636.

Garland, E. L. (2012). Pain processing in the human nervous system: A selective review of nociceptive and biobehavioral pathways. Primary Care: Clinics in Office Practice, 39(3), 561-571.

Garry, M. G., Richardson, J. D., □ Hargreaves, K. (1994). Sodium nitroprusside evokes the release of immunoreactive calcitonin gene-related peptide and substance P from dorsal horn slices via nitric oxide-dependent and nitric oxide-independent mechanisms. Journal of Neuroscience, 14(7), 4329-4337.

Gauriau, C., □ Bernard, J. F. (2002). Pain pathways and parabrachial circuits in the rat. Experimental Physiology, 87(2), 251-258.

Geppetti, P., Veldhuis, N. A., Lieu, T., □ Bunnett, N. W. (2015). G protein-coupled receptors: Dynamic machines for signaling pain and itch. Neuron, 88(4), 635-649.

Ghalandari-Shamami, M., Hassanpour-Ezatti, M., □ Haghparast, A. (2011). Intra-accumbal NMDA but not AMPA□kainate receptor antagonist attenuates WIN55, 212-2 cannabinoid receptor agonist-induced antinociception in the basolateral amygdala in a rat model of acute pain. Pharmacology Biochemistry and Behavior, 100(2), 213-219.

Gilron, I., Bailey, J. M., Tu, D., Holden, R. R., Weaver, D. F., □ Houlden, R. L. (2005). Morphine, gabapentin, or their combination for neuropathic pain. The New England Journal of Medicine, 352(13), 1324-1334.

Gilron, I., □ Max, M. B. (2005). Combination pharmacotherapy for neuropathic pain: Current evidence and future directions. Expert Review of Neurotherapeutics, 5(6), 823-830.

Gilron, I., Watson, C. P., Cahill, C. M., □ Moulin, D. E. (2006). Neuropathic pain: A practical guide for the clinician. Canadian Medical Association Journal, 175(3), 265-275.

Gilsbach, R., □ Hein, L. (2008). Presynaptic metabotropic receptors for acetylcholine and adrenaline□noradrenaline. Handbook of Experimental Pharmacology(184), 261-288.

Giordano, J., □ Schultea, T. (2004). Serotonin 5-HT (3) receptor mediation of pain and anti-nociception: Implications for clinical therapeutics. Pain Physician, 7(1), 141-147.

Glass, M., Faull, R., □ Dragunow, M. (1997). Cannabinoid receptors in the human brain: A detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience, 77(2), 299-318.

Glaum, S. R., Proudfit, H. K., □ Anderson, E. G. (1990). 5-HT 3 receptors modulate spinal nociceptive reflexes. Brain Research, 510(1), 12-16.

Godefroy, F., Weil-Fugazza, J., □ Besson, J. M. (1987). Complex temporal changes in 5-hydroxytryptamine synthesis in the central nervous system induced by experimental polyarthritis in the rat. Pain, 28(2), 223-238.

Gold, M. S., Levine, J. D., □ Correa, A. M. (1998). Modulation of TTX-R I Na by PKC and PKA and their role in PGE2-induced sensitization of rat sensory neurons in vitro. Journal of Neuroscience, 18(24), 10345-10355.

Gold, M. S., Reichling, D. B., Shuster, M. J., □ Levine, J. D. (1996). Hyperalgesic agents increase a tetrodotoxin-resistant Na□ current in nociceptors. Proceedings of the National Academy of Sciences, 93(3), 1108-1112.

Gold, M. S., Weinreich, D., Kim, C.-S., Wang, R., Treanor, J., Porreca, F., & Lai, J. (2003). Redistribution of Nav1. 8 in uninjured axons enables neuropathic pain. Journal of Neuroscience, 23(1), 158-166.

Gopalsamy, B., Farouk, A. A. O., Tengku, T. A. S., Sulaiman, M. R., & Perimal, E. K. (2017). Antiallodynic and antihyperalgesic activities of zerumbone via the suppression of iL-1β, iL-6, and TNF-α in a mouse model of neuropathic pain. Journal of Pain Research, 10, 2605-2619.

Gordaliza, M. (2007). Natural products as leads to anticancer drugs. Clinical and Translational Oncology, 9(12), 767-776.

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(4), 374-385.

Graham, R. M., Perez, D. M., Hwa, J., & Piascik, M. T. (1996). Alpha 1-adrenergic receptor subtypes. Molecular structure, function, and signaling. Circulation Research, 78(5), 737-749.

Grudt, T. J., Williams, J. T., & Travagli, R. A. (1995). Inhibition by 5-hydroxytryptamine and noradrenaline in substantia gelatinosa of guinea-pig spinal trigeminal nucleus. The Journal of Physiology, 485(1), 113-120.

Gruner, J. A. (1992). A monitored contusion model of spinal cord injury in the rat. Journal of Neurotrauma, 9(2), 123-126; discussion 126-128.

Guimaraes, S., & Moura, D. (2001). Vascular adrenoceptors: An update. Pharmacological Reviews, 53(2), 319-356.

Guindon, J., & Hohmann, A. (2008). Cannabinoid CB2 receptors: A therapeutic target for the treatment of inflammatory and neuropathic pain. British Journal of Pharmacology, 153(2), 319-334.

Guo, W., Robbins, M. T., Wei, F., Zou, S., Dubner, R., & Ren, K. (2006). Supraspinal brain-derived neurotrophic factor signaling: A novel mechanism for descending pain facilitation. Journal of Neuroscience, 26(1), 126-137.

Gutierrez, T., Nackley, A. G., Neely, M. H., Freeman, K. G., Edwards, G. L., & Hohmann, A. G. (2003). Effects of neurotoxic destruction of descending noradrenergic pathways on cannabinoid antinociception in models of acute and tonic nociception. Brain Research, 987(2), 176-185.

Gyires, K., Zadori, Z. S., Torok, T., Matyus, P. (2009). Alpha(2)-adrenoceptor subtypes-mediated physiological, pharmacological actions. Neurochemistry International, 55(7), 447-453.

Hains, B. C., Willis, W. D., Hulsebosch, C. E. (2003). Serotonin receptors 5-HT1a and 5-HT3 reduce hyperexcitability of dorsal horn neurons after chronic spinal cord hemisection injury in rat. Experimental Brain Research, 149(2), 174-186.

Hajhashemi, V., Banafshe, H. R., Minaiyan, M., Mesdaghinia, A., Abed, A. (2014). Antinociceptive effects of venlafaxine in a rat model of peripheral neuropathy: Role of alpha2-adrenergic receptors. European Journal of Pharmacology, 738, 230-236.

Hald, A. (2009). Spinal astrogliosis in pain models: Cause and effects. Cellular and Molecular Neurobiology, 29(5), 609-619.

Hall, J. E., Uhrich, T. D., Barney, J. A., Arain, S. R., Ebert, T. J. (2000). Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesthesia Analgesia, 90(3), 699-705.

Hannon, J., Hoyer, D. (2002). Serotonin receptors and systems: Endless diversity. Acta Biologica Szegediensis, 46(1-2), 1-12.

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(1), 77-88.

Hartrick, C. T. (2012). Noradrenergic reuptake inhibition in the treatment of pain. Expert Opinion on Investigational Drugs, 21(12), 1827-1834.

Hayashida, K.-i., DeGoes, S., Curry, R., Eisenach, J. C. (2007). Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. Anesthesiology: The Journal of the American Society of Anesthesiologists, 106(3), 557-562.

Heinricher, M., McGaraughty, S., Farr, D. (1999). The role of excitatory amino acid transmission within the rostral ventromedial medulla in the antinociceptive actions of systemically administered morphine. Pain, 81(1), 57-65.

Hendriks, H., Malingr, T. M., Batterman, S., Bos, R. (1975). Mono-and sesqui-terpene hydrocarbons of the essential oil of cannabis sativa. Phytochemistry, 14(3), 814-815.

Herkenham, M., Lynn, A. B., Johnson, M. R., Melvin, L. S., de Costa, B. R., Rice, K. C. (1991). Characterization and localization of cannabinoid

receptors in rat brain: A quantitative in vitro autoradiographic study. Journal of Neuroscience, 11(2), 563-583.

Hernandez, A., Constandil, L., Laurido, C., Pelissier, T., Marchand, F., Ardid, D., Alloui, A., Eschalier, A., □ Soto-Moyano, R. (2004). Venlafaxine-induced depression of wind-up activity in mononeuropathic rats is potentiated by inhibition of brain 5-HT1a receptor expression in vivo. International Journal of Neuroscience, 114(2), 229-242.

Herzberg, U., Eliav, E., Bennett, G. J., □ Kopin, I. J. (1997). The analgesic effects of r(□)-WIN 55,212-2 mesylate, a high affinity cannabinoid agonist, in a rat model of neuropathic pain. Neuroscience Letters, 221(2-3), 157-160.

Hirono, M., Matsunaga, W., Chimura, T., □ Obata, K. (2008). Developmental enhancement of alpha2-adrenoceptor-mediated suppression of inhibitory synaptic transmission onto mouse cerebellar purkinje cells. Neuroscience, 156(1), 143-154.

Ho, Y. C., Lee, S. S., Yang, M. L., Huang-Liu, R., Lee, C. Y., Li, Y. C., □ Kuan, Y. H. (2017). Zerumbone reduced the inflammatory response of acute lung injury in endotoxin-treated mice via Akt-NFkappab pathway. Chemico-Biological Interactions, 271, 9-14.

Holden, J., Farah, E. N., □ Jeong, Y. (2005). Stimulation of the lateral hypothalamus produces antinociception mediated by 5-HT 1a, 5-HT 1b and 5-HT 3 receptors in the rat spinal cord dorsal horn. Neuroscience, 135(4), 1255-1268.

Holden, J., □ Proudfit, H. (1998). Enkephalin neurons that project to the a7 catecholamine cell group are located in nuclei that modulate nociception: Ventromedial medulla. Neuroscience, 83(3), 929-947.

Hong, S., □ Wiley, J. W. (2005). Early painful diabetic neuropathy is associated with differential changes in the expression and function of vanilloid receptor 1. Journal of Biological Chemistry, 280(1), 618-627.

Hong, Y., □ Abbott, F. V. (1996). Contribution of peripheral α1a-adrenoceptors to pain induced by formalin or by α-methyl-5-hydroxytryptamine plus noradrenaline. European Journal of Pharmacology, 301(1), 41-48.

Hord, A. H., Chalfoun, A. G., Denson, D. D., □ Azevedo, M. I. (2001a). Systemic tizanidine hydrochloride (Zanaflex□) relieves thermal hyperalgesia in rats with an experimental mononeuropathy. Anesthesia □ Analgesia, 93(5), 1310-1315.

Hord, A. H., Denson, D. D., Stowe, B., □ Haygood, R. M. (2001b). A-1 and α-2 adrenergic antagonists relieve thermal hyperalgesia in experimental

mononeuropathy from chronic constriction injury. Anesthesia Analgesia, 92(6), 1558-1562.

Hoshino, H., Obata, H., Saito, S. (2015). Antihyperalgesic effect of duloxetine and amitriptyline in rats after peripheral nerve injury: Influence of descending noradrenergic plasticity. Neuroscience Letters, 602, 62-67.

Howe, J. R., Wang, J.-Y., Yaksh, T. L. (1983). Selective antagonism of the antinociceptive effect of intrathecally applied alpha adrenergic agonists by intrathecal prazosin and intrathecal yohimbine. Journal of Pharmacology and Experimental Therapeutics, 224(3), 552-558.

Howlett, A. C., Mukhopadhyay, S. (2000). Cellular signal transduction by anandamide and 2-arachidonoylglycerol. Chemistry and Physics of Lipids, 108(1), 53-70.

Hoyer, D., Clarke, D. E., Fozard, J. R., Hartig, P. R., Martin, G. R., Mylecharane, E. J., Saxena, P. R., Humphrey, P. P. (1994). International union of pharmacology classification of receptors for 5-hydroxytryptamine (serotonin). Pharmacological Reviews, 46(2), 157-203.

Hoyer, D., Hannon, J. P., Martin, G. R. (2002). Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacology Biochemistry and Behavior, 71(4), 533-554.

Huang, J., Chang, J. Y., Woodward, D. J., Baccala, L. A., Han, J. S., Wang, J. Y., Luo, F. (2006). Dynamic neuronal responses in cortical and thalamic areas during different phases of formalin test in rats. Experimental Neurology, 200(1), 124-134.

Hudson, L. J., Bevan, S., McNair, K., Gentry, C., Fox, A., Kuhn, R., Winter, J. (2002). Metabotropic glutamate receptor 5 upregulation in A-fibers after spinal nerve injury: 2-methyl-6-(phenylethynyl)-pyridine (MPEP) reverses the induced thermal hyperalgesia. Journal of Neuroscience, 22(7), 2660-2668.

Hudson, L. J., Bevan, S., Wotherspoon, G., Gentry, C., Fox, A., Winter, J. (2001). VR1 protein expression increases in undamaged drg neurons after partial nerve injury. European Journal of Neuroscience, 13(11), 2105-2114.

Huettner, J. E. (2003). Kainate receptors and synaptic transmission. Progress in Neurobiology, 70(5), 387-407.

Hughes, C. R., Keele, N. B. (2006). Phenytoin normalizes exaggerated fear behavior in p-chlorophenylalanine (PCPA)-treated rats. Epilepsy Behavior, 9(4), 557-563.

Hughes, C. R., Tran, L., □ Keele, N. B. (2012). 5-HT2a receptor activation normalizes exaggerated fear behavior in p-chlorophenylalanine (PCPA)-treated rats. Journal of Behavioral and Brain Science, 2, 454.

Hulse, R., Wynick, D., □ Donaldson, L. F. (2010). Intact cutaneous C fibre afferent properties in mechanical and cold neuropathic allodynia. European Journal of Pain, 14(6), 565 e561-565 e510.

Hunt, S. P., □ Mantyh, P. W. (2001). The molecular dynamics of pain control. Nature Reviews Neuroscience, 2(2), 83-91.

Ibrahim, M. Y., Abdul, A., Ibrahim, T. A. T., Abdelwahab, S. I., Elhassan, M. M., □ Syam, M. (2010). Evaluation of acute toxicity and the effect of single injected doses of zerumbone on the kidney and liver functions in sprague dawley rats. African Journal of Biotechnology, 9(28), 4442-4450.

Id□np□n-Heikkil□, J. J., Kalso, E. A., □ Sepp□1□, T. (1994). Antinociceptive actions of dexmedetomidine and the kappa-opioid agonist u-50,488 h against noxious thermal, mechanical and inflammatory stimuli. Journal of Pharmacology and Experimental Therapeutics, 271(3), 1306-1313.

Irving, G. A. (2005). Contemporary assessment and management of neuropathic pain. Neurology, 64(12 Suppl 3), S21-27.

Ishac, E. J., Jiang, L., Lake, K. D., Varga, K., Abood, M. E., □ Kunos, G. (1996). Inhibition of exocytotic noradrenaline release by presynaptic cannabinoid CB receptors on peripheral sympathetic nerves. British Journal of Pharmacology, 118(8), 2023-2028.

Issemann, I., □ Green, S. (1990). Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature, 347(6294), 645-650.

Iversen, S. D. (1984). 5-HT and anxiety. Neuropharmacology, 23(12B), 1553-1560.

Iyengar, S., Webster, A. A., Hemrick-Luecke, S. K., Xu, J. Y., □ Simmons, R. M. (2004). Efficacy of duloxetine, a potent and balanced serotonin-norepinephrine reuptake inhibitor in persistent pain models in rats. Journal of Pharmacology and Experimental Therapeutics, 311(2), 576-584.

Jackson, K. C., 2nd. (2006). Pharmacotherapy for neuropathic pain. Pain Practice, 6(1), 27-33.

Jackson, S. M., Parhami, F., Xi, X.-P., Berliner, J. A., Hsueh, W. A., Law, R. E., □ Demer, L. L. (1999). Peroxisome proliferator□activated receptor activators target human endothelial cells to inhibit leukocyte□endothelial

cell interaction. Arteriosclerosis, Thrombosis, and Vascular Biology, 19(9), 2094-2104.

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

Jantan, I. b., Yassin, M. S. M., Chin, C. B., Chen, L. L., Sim, N. L. (2003). Antifungal activity of the essential oils of nine zingiberaceae species. Pharmaceutical Biology, 41(5), 392-397.

Ji, R.-R., Baba, H., Brenner, G. J., Woolf, C. J. (1999). Nociceptive-specific activation of erk in spinal neurons contributes to pain hypersensitivity. Nature Neuroscience, 2(12), 1114-1119.

Ji, R.-R., Samad, T. A., Jin, S.-X., Schmoll, R., Woolf, C. J. (2002). P38 mapk activation by NGF in primary sensory neurons after inflammation increases TRPV1 levels and maintains heat hyperalgesia. Neuron, 36(1), 57-68.

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(12), 696-705.

Jiang, C., Ting, A. T., Seed, B. (1998). PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature, 391(6662), 82-86.

Johnson, J. R., Burnell-Nugent, M., Lossignol, D., Ganae-Motan, E. D., Potts, R., Fallon, M. T. (2010). Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. Journal of Pain and Symptom Management, 39(2), 167-179.

Joshi, I., Taylor, C. P. (2006). Pregabalin action at a model synapse: Binding to presynaptic calcium channel α 2-δ subunit reduces neurotransmission in mice. European Journal of Pharmacology, 553(1), 82-88.

Kala, C. P., Dhyani, P. P., Sajwan, B. S. (2006). Developing the medicinal plants sector in northern India: Challenges and opportunities. Journal of Ethnobiology and Ethnomedicine, 2, 32-32.

Kanai, Y., Nakazato, E., Fujiuchi, A., Hara, T., Imai, A. (2005). Involvement of an increased spinal TRPV1 sensitization through its up-regulation in mechanical allodynia of cci rats. Neuropharmacology, 49(7), 977-984.

Kandhare, A. D., Raygude, K. S., Ghosh, P., Ghule, A. E., Bodhankar, S. L. (2012). Neuroprotective effect of naringin by modulation of endogenous

biomarkers in streptozotocin induced painful diabetic neuropathy. Fitoterapia, 83(4), 650-659.

Kapoor, L. (1990). CRC handbook of ayurvedic medicinal plants. Poca Raton, FL: CRC Press Google Scholar.

Kato, H., Narita, M., Miyatake, M., Yajima, Y., Suzuki, T. (2006). Role of neuronal nr2b subunit-containing NMDA receptor-mediated Ca2 influx and astrocytic activation in cultured mouse cortical neurons and astrocytes. Synapse, 59(1), 10-17.

Kaur, P., Muthuraman, A., Kaur, J. (2015). Ameliorative potential of angiotensin-converting enzyme inhibitor (ramipril) on chronic constriction injury of sciatic nerve induced neuropathic pain in mice. Journal of the Renin-Angiotensin-Aldosterone System, 16(1), 103-112.

Kaushal, R., Taylor, B., Jamal, A., Zhang, L., Ma, F., Donahue, R., Westlund, K. (2016). GABA-a receptor activity in the noradrenergic locus coeruleus drives trigeminal neuropathic pain in the rat; contribution of Nα1 receptors in the medial prefrontal cortex. Neuroscience, 334, 148-159.

Kawasaki, Y., Kumamoto, E., Furue, H., Yoshimura, M. (2003). Alpha 2 adrenoceptor-mediated presynaptic inhibition of primary afferent glutamatergic transmission in rat substantia gelatinosa neurons. Anesthesiology, 98(3), 682-689.

Kawasaki, Y., Zhang, L., Cheng, J.-K., Ji, R.-R. (2008). Cytokine mechanisms of central sensitization: Distinct and overlapping role of interleukin-1β, interleukin-6, and tumor necrosis factor-α in regulating synaptic and neuronal activity in the superficial spinal cord. Journal of Neuroscience, 28(20), 5189-5194.

Kayser, V., Aubel, B., Hamon, M., Bourgoin, S. (2002). The antimigraine 5-HT 1b 1d receptor agonists, sumatriptan, zolmitriptan and dihydroergotamine, attenuate pain-related behaviour in a rat model of trigeminal neuropathic pain. British Journal of Pharmacology, 137(8), 1287-1297.

Kayser, V., Besson, J.-M., Guilbaud, G. (1992a). Evidence for a noradrenergic component in the antinociceptive effect of the analgesic agent tramadol in an animal model of clinical pain, the arthritic rat. European Journal of Pharmacology, 224(1), 83-88.

Kayser, V., Desmeules, J., Guilbaud, G. (1995). Systemic clonidine differentially modulates the abnormal reactions to mechanical and thermal stimuli in rats with peripheral mononeuropathy. Pain, 60(3), 275-285.

Kayser, V., Guilbaud, G., Besson, J. (1992b). Potent antinociceptive effects of clonidine systemically administered in an experimental model of clinical pain, the arthritic rat. Brain Research, 593(1), 7-13.

Kerstman, E., Ahn, S., Battu, S., Tariq, S., Grabois, M. (2013). Neuropathic pain. Handbook of Clinical Neurology, 110, 175-187.

Khalid, M. H., Akhtar, M. N., Mohamad, A. S., Perimal, E. K., Akira, A., Israf, D. A., Lajis, N., Sulaiman, M. R. (2011). Antinociceptive effect of the essential oil of zingiber zerumbet in mice: Possible mechanisms. Journal of Ethnopharmacology, 137(1), 345-351.

Kiguchi, N., Maeda, T., Kobayashi, Y., Fukazawa, Y., Kishioka, S. (2010). Macrophage inflammatory protein-1α mediates the development of neuropathic pain following peripheral nerve injury through interleukin-1β up-regulation. PAIN, 149(2), 305-315.

Kim, H. J., Na, H. S., Back, S. K., Hong, S. K. (2001). Sympathetic sprouting in sensory ganglia depends on the number of injured neurons. Neuroreport, 12(16), 3529-3532.

Kim, J. W., Jeong, H., Yang, M. S., Lim, C. W., Kim, B. (2017). Therapeutic effects of zerumbone in an alkali-burned corneal wound healing model. International Immunopharmacology, 48, 126-134.

Kim, S. H., Chung, J. M. (1992). An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain, 50(3), 355-363.

Kim, S. K., Min, B.-I., Kim, J. H., Hwang, B. G., Yoo, G. Y., Park, D. S., Na, H. S. (2005). Effects of α1- and α2-adrenoreceptor antagonists on cold allodynia in a rat tail model of neuropathic pain. Brain Research, 1039(1), 207-210.

Kissin, I. (2010). The development of new analgesics over the past 50 years: A lack of real breakthrough drugs. Anesthesia Analgesia, 110(3), 780-789.

Kitto, K. F., Haley, J. E., Wilcox, G. L. (1992). Involvement of nitric oxide in spinally mediated hyperalgesia in the mouse. Neuroscience Letters, 148(1), 1-5.

Klayman, D. L. (1985). inghaosu (artemisinin): An antimalarial drug from China. Science, 228, 1049-1056.

Knotkova, H., Pappagallo, M. (2007). Adjuvant analgesics. Anesthesiology Clinics, 25(4), 775-786, vi.

Knowlton, W. M., Daniels, R. L., Palkar, R., McCoy, D. D., & McKemy, D. D. (2011). Pharmacological blockade of TRPM8 ion channels alters cold and cold pain responses in mice. PLOS ONE, 6(9), e25894.

Koch, S., Hemrick-Luecke, S. K., Thompson, L. K., Evans, D. C., Threlkeld, P. G., Nelson, D. L., Perry, K. W., & Bymaster, F. P. (2003). Comparison of effects of dual transporter inhibitors on monoamine transporters and extracellular levels in rats. Neuropharmacology, 45(7), 935-944.

Koga, K., Chen, T., Li, X. Y., Descalzi, G., Ling, J., Gu, J., & Zhuo, M. (2011). Glutamate acts as a neurotransmitter for gastrin releasing peptide-sensitive and insensitive itch-related synaptic transmission in mammalian spinal cord. Molecular Pain, 7, 47.

Koneru, A., Satyanarayana, S., & Rizwan, S. (2009). Endogenous opioids: Their physiological role and receptors. Global Journal of Pharmacology, 3(3), 149-153.

Kota, B. P., Huang, T. H., & Roufogalis, B. D. (2005). An overview on biological mechanisms of PPARs. Pharmacological Research, 51(2), 85-94.

Kroeze, W. K., Kristiansen, K., & Roth, B. L. (2002). Molecular biology of serotonin receptors structure and function at the molecular level. Current Topics in Medicinal Chemistry, 2(6), 507-528.

Kuhad, A., Sharma, S., & Chopra, K. (2008). Lycopene attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. European Journal of Pain, 12(5), 624-632.

Kumar, V. M., Vetrivelan, R., & Mallick, H. N. (2007). Noradrenergic afferents and receptors in the medial preoptic area: Neuroanatomical and neurochemical links between the regulation of sleep and body temperature. Neurochemistry International, 50(6), 783-790.

Kutsuwada, T., Kashiwabuchi, N., Mori, H., Sakimura, K., Kushiya, E., Araki, K., Meguro, H., Masaki, H., Kumanishi, T., Arakawa, M., & et al. (1992). Molecular diversity of the NMDA receptor channel. Nature, 358(6381), 36-41.

Kwan, K. Y., Allchorne, A. J., Vollrath, M. A., Christensen, A. P., Zhang, D. S., Woolf, C. J., & Corey, D. P. (2006). TRPA1 contributes to cold, mechanical, and chemical nociception but is not essential for hair-cell transduction. Neuron, 50(2), 277-289.

Lai, J., Hunter, J. C., & Porreca, F. (2003). The role of voltage-gated sodium channels in neuropathic pain. Current Opinion in Neurobiology, 13(3), 291-297.

Laird, J. M., Bennett, G. J. (1993). An electrophysiological study of dorsal horn neurons in the spinal cord of rats with an experimental peripheral neuropathy. Journal of Neurophysiology, 69(6), 2072-2085.

Langford, R. M., Mares, J., Novotna, A., Vachova, M., Novakova, I., Notcutt, W., Ratcliffe, S. (2013). A double-blind, randomized, placebo-controlled, parallel-group study of thc cbd oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. Journal of Neurology, 260(4), 984-997.

Laporte, A., Fattaccini, C., Lombard, M., Chauveau, J., Hamon, M. (1995). Effects of dorsal rhizotomy and selective lesion of serotonergic and noradrenergic systems on 5-HT 1a, 5-HT 1b and 5-HT 3 receptors in the rat spinal cord. Journal of Neural Transmission, 100(3), 207-223.

Larsen, K., Ibrahim, H., Khaw, S., Saw, L. (1999). Gingers of peninsular malaysia and singapore: Natural History Publications (Borneo).

Lauder, J. M., Liu, J., Grayson, D. R. (2000). In utero exposure to serotonergic drugs alters neonatal expression of 5-HT 1a receptor transcripts: A quantitative rt-pcr study. International Journal of Developmental Neuroscience, 18(2), 171-176.

Laurie, D. J., Bartke, I., Schoepfer, R., Naujoks, K., Seeburg, P. H. (1997). Regional, developmental and interspecies expression of the four NMDAr2 subunits, examined using monoclonal antibodies. Molecular Brain Research, 51(1), 23-32.

Le Bars, D., Dickenson, A. H., Besson, J. M. (1979a). Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain, 6(3), 283-304.

Le Bars, D., Dickenson, A. H., Besson, J. M. (1979b). Diffuse noxious inhibitory controls (DNIC). Ii. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. Pain, 6(3), 305-327.

Le Bars, D., Villanueva, L., Bouhassira, D., Willer, J. C. (1992). Diffuse noxious inhibitory controls (DNIC) in animals and in man. Patologicheskaia Fiziologiia I Eksperimental naia Terapiia(4), 55-65.

Lee, D. H., Liu, X., Kim, H. T., Chung, K., Chung, J. M. (1999). Receptor subtype mediating the adrenergic sensitivity of pain behavior and ectopic discharges in neuropathic lewis rats. Journal of Neurophysiology, 81(5), 2226-2233.

Lee, H. G., Choi, J. I., Kim, Y. O., Yoon, M. H. (2013). The role of alpha-2 adrenoceptor subtype in the antiallodynic effect of intraplantar

dexmedetomidine in a rat spinal nerve ligation model. Neuroscience Letters, 557 Pt B, 118-122.

Lee, Y.-H., Ryu, T.-G., Park, S.-J., Yang, E.-J., Jeon, B.-H., Hur, G.-M., Kim, K.-J. (2000). A1-adrenoceptors involvement in painful diabetic neuropathy: A role in allodynia. Neuroreport, 11(7), 1417-1420.

Leiphart, J. W., Dills, C. V., Zikel, O. M., Kim, D. L., Levy, R. M. (1995). A comparison of intrathecally administered narcotic and nonnarcotic analgesics for experimental chronic neuropathic pain. Journal of Neurosurgery, 82(4), 595-599.

Leung, W. S., Yang, M. L., Lee, S. S., Kuo, C. W., Ho, Y. C., Huang-Liu, R., Lin, H. W., Kuan, Y. H. (2017). Protective effect of zerumbone reduces lipopolysaccharide-induced acute lung injury via antioxidative enzymes and Nrf2HO-1 pathway. International Immunopharmacology, 46, 194-200.

Levy, D., Zochodne, D. W. (2004). No pain: Potential roles of nitric oxide in neuropathic pain. Pain Practice, 4(1), 11-18.

Li, J. L., Kaneko, T., Nomura, S., Li, Y. ., Mizuno, N. (1997). Association of serotonin-like immunoreactive axons with nociceptive projection neurons in the caudal spinal trigeminal nucleus of the rat. Journal of Comparative Neurology, 384(1), 127-141.

Li, S., Han, J., Wang, D.-s., Feng, B., Deng, Y.-t., Wang, X.-s., Yang, ., Zhao, M.-g. (2016). Echinocystic acid reduces reserpine-induced paindepression dyad in mice. Metabolic Brain Disease, 31(2), 455-463.

Li, S.-F., Zhang, Y.-Y., Li, Y.-Y., Wen, S., Xiao, Z. (2014). Antihyperalgesic effect of 5-HT 7 receptor activation on the midbrain periaqueductal gray in a rat model of neuropathic pain. Pharmacology Biochemistry and Behavior, 127, 49-55.

Lichtman, A. H., Martin, B. R. (1991a). Cannabinoid-induced antinociception is mediated by a spinalα 2-noradrenergic mechanism. Brain Research, 559(2), 309-314.

Lichtman, A. H., Martin, B. R. (1991b). Spinal and supraspinal components of cannabinoid-induced antinociception. Journal of Pharmacology and Experimental Therapeutics, 258(2), 517-523.

Light, A. R., Shults, R. C., Jones, S. L. (1992). The initial processing of pain and its descending control: Spinal and trigeminal systems: Karger Basel.

Linton, S. J. (2000). A review of psychological risk factors in back and neck pain. Spine, 25(9), 1148-1156.

Liu, F. Y., Xing, G. G., □u, X. X., Xu, I. S., Han, J. S., □ Wan, Y. (2007). Roles of 5-hydroxytryptamine (5-HT) receptor subtypes in the inhibitory effects of 5-HT on C-fiber responses of spinal wide dynamic range neurons in rats. Journal of Pharmacology and Experimental Therapeutics, 321(3), 1046-1053.

Liu, W. Y., Tzeng, T. F., □ Liu, I. M. (2017). Healing potential of zerumbone ointment on experimental full-thickness excision cutaneous wounds in rat. Journal of Tissue Viability, 26(3), 202-207.

LoVerme, J., Fu, J., Astarita, G., La Rana, G., Russo, R., Calignano, A., □ Piomelli, D. (2005). The nuclear receptor peroxisome proliferator-activated receptor-α mediates the anti-inflammatory actions of palmitoylethanolamide. Molecular Pharmacology, 67(1), 15-19.

LoVerme, J., Russo, R., La Rana, G., Fu, J., Farthing, J., Mattace-Raso, G., Meli, R., Hohmann, A., Calignano, A., □ Piomelli, D. (2006). Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor-α. Journal of Pharmacology and Experimental Therapeutics, 319(3), 1051-1061.

Lu, J.-J., Pan, W., Hu, Y.-J., □ Wang, Y.-T. (2012). Multi-target drugs: The trend of drug research and development. PLOS ONE, 7(6), e40262.

Lu, Y., □ Perl, E. R. (2003). A specific inhibitory pathway between substantia gelatinosa neurons receiving direct C-fiber input. Journal of Neuroscience, 23(25), 8752-8758.

Ma, C., Shu, Y., Zheng, Z., Chen, Y., Yao, H., Greenquist, K. W., White, F. A., □ LaMotte, R. H. (2003). Similar electrophysiological changes in axotomized and neighboring intact dorsal root ganglion neurons. Journal of Neurophysiology, 89(3), 1588-1602.

Mackie, K. (2005). Distribution of cannabinoid receptors in the central and peripheral nervous system. Cannabinoids, 299-325.

Mackie, K., □ Hille, B. (1992). Cannabinoids inhibit N-type calcium channels in neuroblastoma-glioma cells. Proceedings of the National Academy of Sciences, 89(9), 3825-3829.

Maeda, T., Kiguchi, N., Kobayashi, Y., Ozaki, M., □ Kishioka, S. (2008). Pioglitazone attenuates tactile allodynia and thermal hyperalgesia in mice subjected to peripheral nerve injury. Journal of Pharmacological Sciences, 108(3), 341-347.

Maeda, T., □ Kishioka, S. (2009). PPAR and pain. International Review of Neurobiology, 85, 165-177.

Maggi, L. B., Sadeghi, H., Weigand, C., Scarim, A. L., Heitmeier, M. R., Corbett, J. A. (2000). Anti-inflammatory actions of 15-deoxy-delta 12, 14-prostaglandin j2 and troglitazone: Evidence for heat shock-dependent and-independent inhibition of cytokine-induced inducible nitric oxide synthase expression. Diabetes, 49(3), 346-355.

Mahato, S. B., Nandy, A. K., Roy, G. (1992). Triterpenoids. Phytochemistry, 31(7), 2199-2249.

Malinow, R., Madison, D. V., Tsien, R. W. (1988). Persistent protein kinase activity underlying long-term potentiation. Nature, 335(6193), 820-824.

Mangelsdorf, D. J., Evans, R. M. (1995). The RXR heterodimers and orphan receptors. Cell, 83(6), 841-850.

Mannion, R., Costigan, M., Decosterd, I., Amaya, F., Ma, .-P., Holstege, J., Ji, R.-R., Acheson, A., Lindsay, R., Wilkinson, G. (1999). Neurotrophins: Peripherally and centrally acting modulators of tactile stimulus-induced inflammatory pain hypersensitivity. Proceedings of the National Academy of Sciences, 96(16), 9385-9390.

Mansouri, M. T., Naghizadeh, B., Ghorbanzadeh, B., Rajabi, H., Pashmforoush, M. (2017). Pharmacological evidence for systemic and peripheral antinociceptive activities of pioglitazone in the rat formalin test: Role of PPARγ and nitric oxide. European Journal of Pharmacology, 805, 84-92.

Mantyh, P. W. (2002). Neurobiology of substance P and the NK1 receptor. Journal of Clinical Psychiatry, 63 Suppl 11, 6-10.

Mao, J., Price, D. D., Hayes, R. L., Lu, J., Mayer, D. J., Frenk, H. (1993). Intrathecal treatment with dextrorphan or ketamine potently reduces pain-related behaviors in a rat model of peripheral mononeuropathy. Brain Research, 605(1), 164-168.

Mao, .-., Huang, Z., Ip, S.-P., Xian, Y.-F., Che, C.-T. (2011). Role of 5-HT1a and 5-HT1b receptors in the antidepressant-like effect of piperine in the forced swim test. Neuroscience Letters, 504(2), 181-184.

Marlier, L., Sandillon, F., Poulat, P., Rajaofetra, N., Geffard, M., Privat, A. (1991). Serotonergic innervation of the dorsal horn of rat spinal cord: Light and electron microscopic immunocytochemical study. Journal of Neurocytology, 20(4), 310-322.

Marrone, M. C., Morabito, A., Giustizieri, M., Chiurchi, V., Leuti, A., Mattioli, M., Marinelli, S., Riganti, L., Lombardi, M., Murana, E., Totaro, A., Piomelli, D., Ragozzino, D., Oddi, S., Maccarrone, M., Verderio, C., Marinelli, S. (2017). TRPV1 channels are critical brain inflammation

detectors and neuropathic pain biomarkers in mice. Nature Communications, 8, 15292.

Martin, K. F., Hannon, S., Phillips, I., □ Heal, D. J. (1992). Opposing roles for 5-HT1b and 5-HT3 receptors in the control of 5-HT release in rat hippocampus in vivo. British Journal of Pharmacology, 106(1), 139-142.

Martin, W. J., Coffin, P. O., Attias, E., Balinsky, M., Tsou, K., □ Walker, J. M. (1999). Anatomical basis for cannabinoid-induced antinociception as revealed by intracerebral microinjections. Brain Research, 822(1), 237-242.

Martin, W. J., Tsou, K., □ Walker, J. M. (1998). Cannabinoid receptor-mediated inhibition of the rat tail-flick reflex after microinjection into the rostral ventromedial medulla. Neuroscience Letters, 242(1), 33-36.

Martins, I., Carvalho, P., de Vries, M. G., Teixeira-Pinto, A., Wilson, S. P., Westerink, B. H., □ Tavares, I. (2015). Increased noradrenergic neurotransmission to a pain facilitatory area of the brain is implicated in facilitation of chronic pain. Anesthesiology: The Journal of the American Society of Anesthesiologists, 123(3), 642-653.

Martucci, C., Trovato, A. E., Costa, B., Borsani, E., Franchi, S., Magnaghi, V., Panerai, A. E., Rodella, L. F., Valsecchi, A. E., Sacerdote, P., □ Colleoni, M. (2008). The purinergic antagonist ppads reduces pain related behaviours and interleukin-1 beta, interleukin-6, inos and nnos overproduction in central and peripheral nervous system after peripheral neuropathy in mice. Pain, 137(1), 81-95.

Maruo, K., Yamamoto, H., Yamamoto, S., Nagata, T., Fujikawa, H., Kanno, T., Yaguchi, T., Maruo, S., Yoshiya, S., □ Nishizaki, T. (2006). Modulation of P2X receptors via adrenergic pathways in rat dorsal root ganglion neurons after sciatic nerve injury. Pain, 120(1), 106-112.

Mason, P. (2005). Ventromedial medulla: Pain modulation and beyond. Journal of Comparative Neurology, 493(1), 2-8.

Matsuda, L. A., Lolait, S. J., Brownstein, M. J., Young, A. C., □ Bonner, T. I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature, 346(6284), 561-564.

Max, M. B., Byas-Smith, M. G., Gracely, R. H., □ Bennett, G. J. (1995). Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: A double-blind comparison to alfentanil and placebo. Clinical Neuropharmacology, 18(4), 360-368.

McCune, S. K., Voigt, M. M., □ Hill, J. M. (1993). Expression of multiple alpha adrenergic receptor subtype messenger rnas in the adult rat brain. Neuroscience, 57(1), 143-151.

McLachlan, E. M., Janig, W., Devor, M., □ Michaelis, M. (1993). Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. Nature, 363(6429), 543-546.

Mechoulam, R., Ben-Shabat, S., Hanus, L., Ligumsky, M., Kaminski, N. E., Schatz, A. R., Gopher, A., Almog, S., Martin, B. R., Compton, D. R., □ et al. (1995). Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochemical Pharmacology, 50(1), 83-90.

Medzhitov, R. (2008). Origin and physiological roles of inflammation. Nature, 454(7203), 428-435.

Melzack, R. (1996). Gate control theory. Pain Forum, 5(2), 128-138.

Melzack, R., □ Wall, P. D. (1965). Pain mechanisms: A new theory. Science, 150(3699), 971-979.

Mendiguren, A., □ Pineda, J. (2009). Effect of the CB1 receptor antagonists rimonabant and am251 on the firing rate of dorsal raphe nucleus neurons in rat brain slices. British Journal of Pharmacology, 158(6), 1579-1587.

Meng, I. D., Manning, B. H., Martin, W. J., □ Fields, H. L. (1998). An analgesia circuit activated by cannabinoids. Nature, 395(6700), 381-383.

Meng, X. W., Budra, B., Skinner, K., Ohara, P., □ Fields, H. (1997). Noradrenergic input to nociceptive modulatory neurons in the rat rostral ventromedial medulla. Journal of Comparative Neurology, 377(3), 381-391.

Merskey, H., Albe-Fessard, D. G., Bonica, J. J., Carmon, A., Dubner, R., □ Kerr, F. W. L. (1979). Pain terms: A list with definitions and notes on usage. Recommended by the iasp subcommittee on taxonomy. Pain, 6(3), 249.

Michel, M. C., □ Vrydag, W. (2006). Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. British Journal of Pharmacology, 147 Suppl 2, S88-119.

Mika, J., Jurga, A., Starnowska, J., Wasylewski, M., Rojewska, E., Makuch, W., Kwiatkowski, K., Malek, N., □ Przewlocka, B. (2015). Effects of chronic doxepin and amitriptyline administration in na□ve mice and in neuropathic pain mice model. Neuroscience, 294, 38-50.

Miki, K., Zhou, □.-□., Guo, W., Guan, Y., Terayama, R., Dubner, R., □ Ren, K. (2002). Changes in gene expression and neuronal phenotype in brain stem pain modulatory circuitry after inflammation. Journal of Neurophysiology, 87(2), 750-760.

Millan, M. J. (1999). The induction of pain: An integrative review. Progress in Neurobiology, 57(1), 1-164.

Millan, M. J. (2002). Descending control of pain. Progress in Neurobiology, 66(6), 355-474.

Miller, L. H., □ Su, X. (2011). Artemisinin: Discovery from the chinese herbal garden. Cell, 146(6), 855-858.

Mittal, N., Joshi, R., Hota, D., □ Chakrabarti, A. (2009). Evaluation of antihyperalgesic effect of curcumin on formalin-induced orofacial pain in rat. Phytotherapy Research, 23(4), 507-512.

Molina-**Holgado, E., Vela, J. M., Ar□valo-Mart□n, A., Almaz□n, G., Molina-Holgado, F., Borrell, J., □ Guaza, C. (2002). Cannabinoids promote oligodendrocyte progenitor survival: Involvement of cannabinoid receptors and phosphatidylinositol-3 kinase□akt signaling. Journal of Neuroscience, 22(22), 9742-9753.**

Momin, A., □ McNaughton, P. A. (2009). Regulation of firing frequency in nociceptive neurons by pro-inflammatory mediators. Experimental Brain Research, 196(1), 45-52.

Monhemius, R., Azami, J., Green, D., □ Roberts, M. (2001). CB1 receptor mediated analgesia from the nucleus reticularis gigantocellularis pars alpha is activated in an animal model of neuropathic pain. Brain Research, 908(1), 67-74.

Moore, R. A., Derry, S., Aldington, D., Cole, P., □ Wiffen, P. J. (2015). Amitriptyline for neuropathic pain in adults. The Cochrane Database of Systematic Reviews(7), CD008242.

Morel, V., Pickering, G., Etienne, M., Dupuis, A., Privat, A. M., Chalus, M., Eschalier, A., □ Daulhac, L. (2014). Low doses of dextromethorphan have a beneficial effect in the treatment of neuropathic pain. Fundamental □ Clinical Pharmacology, 28(6), 671-680.

Morgenweck, J., Abdel-Aleem, O., McNamara, K., Donahue, R., Badr, M., □ Taylor, B. (2010). Activation of peroxisome proliferator-activated receptor γ in brain inhibits inflammatory pain, dorsal horn expression of fos, and local edema. Neuropharmacology, 58(2), 337-345.

Munro, S., Thomas, K. L., Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. Nature, 365(6441), 61-65.

Muntoni, A. L., Pillolla, G., Melis, M., Perra, S., Gessa, G. L., Pistis, M. (2006). Cannabinoids modulate spontaneous neuronal activity and evoked inhibition of locus coeruleus noradrenergic neurons. European Journal of Neuroscience, 23(9), 2385-2394.

Murakami, A., Takahashi, D., Kinoshita, T., Koshimizu, K., Kim, H. W., Yoshihiro, A., Nakamura, Y., Jiwajinda, S., Terao, J., Ohigashi, H. (2002). Zerumbone, a southeast asian ginger sesquiterpene, markedly suppresses free radical generation, proinflammatory protein production, and cancer cell proliferation accompanied by apoptosis: The alpha,beta-unsaturated carbonyl group is a prerequisite. Carcinogenesis, 23(5), 795-802.

Murakami, A., Takahashi, M., Jiwajinda, S., Koshimizu, K., Ohigashi, H. (1999). Identification of zerumbone in zingiber zerumbet smith as a potent inhibitor of 12-o-tetradecanoylphorbol-13-acetate-induced epstein-barr virus activation. Bioscience, Biotechnology, and Biochemistry, 63(10), 1811-1812.

Musacchio, J. (2013). Chapter 1: Enzymes involved in the biosynthesis and degradation of catecholamines. Iverson L. Biochemistry of Biogenic Amines. Springer, 1-35.

Muthuraman, A., Singh, N., Jaggi, A. S., Ramesh, M. (2014). Drug therapy of neuropathic pain: Current developments and future perspectives. Current Drug Targets, 15(2), 210-253.

Nadal, X., La Porta, C., Andreea Bura, S., Maldonado, R. (2013). Involvement of the opioid and cannabinoid systems in pain control: New insights from knockout studies. European Journal of Pharmacology, 716(1-3), 142-157.

Nader, N. D., Ignatowski, T. A., Kurek, C. J., Knight, P. R., Spengler, R. N. (2001). Clonidine suppresses plasma and cerebrospinal fluid concentrations of tnf-alpha during the perioperative period. Anesthesia Analgesia, 93(2), 363-369 , 363rd contents page.

Nagatsu, T., Levitt, M., Udenfriend, S. (1964). Tyrosine hydroxylase. The initial step in norepinephrine biosynthesis. Journal of Biological Chemistry, 239, 2910-2917.

Nakai, K., Nakae, A., Oba, S., Mashimo, T., Ueda, K. (2010). 5-HT2c receptor agonists attenuate pain-related behaviour in a rat model of trigeminal neuropathic pain. European Journal of Pain, 14(10), 999-1006.

Nakajima, K., Obata, H., Iriuchijima, N., Saito, S. (2012). An increase in spinal cord noradrenaline is a major contributor to the antihyperalgesic effect of antidepressants after peripheral nerve injury in the rat. Pain, 153(5), 990-997.

Nakamura, T., Ikeda, T., Takeda, R., Igawa, K., Naono-Nakayama, R., Sakoda, S., Nishimori, T., Ishida, Y. (2014). The role of spinal serotonin receptor and alpha adrenoceptor on the antiallodynic effects induced by intrathecal milnacipran in chronic constriction injury rats. European Journal of Pharmacology, 738, 57-65.

Nam, T. S., Yeon, D. S., Leem, J. W., Paik, K. S. (2000). Adrenergic sensitivity of uninjured c-fiber nociceptors in neuropathic rats. Yonsei Medical Journal, 41(2), 252-257.

Nassini, R., Materazzi, S., Benemei, S., Geppetti, P. (2014). The TRPA1 channel in inflammatory and neuropathic pain and migraine. Reviews of Physiology, Biochemistry and Pharmacology, 167, 1-43.

Nayak, S., Ronde, P., Spier, A., Lummis, S., Nichols, R. (1999). Calcium changes induced by presynaptic 5-hydroxytryptamine-3 serotonin receptors on isolated terminals from various regions of the rat brain. Neuroscience, 91(1), 107-117.

Neumann, S., Braz, J. M., Skinner, K., Llewellyn-Smith, I. J., Basbaum, A. I. (2008). Innocuous, not noxious, input activates pkcgamma interneurons of the spinal dorsal horn via myelinated afferent fibers. Journal of Neuroscience, 28(32), 7936-7944.

Newman, D. J., Cragg, G. M. (2012). Natural products as sources of new drugs over the 30 years from 1981 to 2010. Journal of Natural Products, 75(3), 311-335.

Newman, D. J., Cragg, G. M. (2016). Natural products as sources of new drugs from 1981 to 2014. Journal of Natural Products, 79(3), 629-661.

Nicholas, A. P., Hokfelt, T., Pieribone, V. A. (1996). The distribution and significance of cns adrenoceptors examined with in situ hybridization. Trends in Pharmacological Sciences, 17(7), 245-255.

Nikolajsen, L., Hansen, C. L., Nielsen, J., Keller, J., Arendt-Nielsen, L., Jensen, T. S. (1996). The effect of ketamine on phantom pain: A central neuropathic disorder maintained by peripheral input. Pain, 67(1), 69-77.

Nilius, B., Owsianik, G., Voets, T., Peters, J. A. (2007). Transient receptor potential cation channels in disease. Physiological Reviews, 87(1), 165-217.

Nishiyama, T. (2005). Effects of a 5-HT2a receptor antagonist, sarpogrelate on thermal or inflammatory pain. European Journal of Pharmacology, 516(1), 18-22.

North, R. A., Yoshimura, M. (1984). The actions of noradrenaline on neurones of the rat substantia gelatinosa in vitro. The Journal of Physiology, 349, 43-55.

Norulaini, N. N., Anuar, O., Omar, A., AlKarkhi, A. F., Setianto, W. B., Fatehah, M., Sahena, F., Zaidul, I. (2009). Optimization of SC-CO 2 extraction of zerumbone from zingiber zerumbet (l) smith. Food Chemistry, 114(2), 702-705.

Nuclear Receptors Nomenclature, C. (1999). A unified nomenclature system for the nuclear receptor superfamily. Cell, 97(2), 161-163.

O'Connor, A. B., Dworkin, R. H. (2009). Treatment of neuropathic pain: An overview of recent guidelines. The American Journal of Medicine, 122(10 Suppl), S22-32.

O'Sullivan, S. E., Kendall, D. A. (2010). Cannabinoid activation of peroxisome proliferator-activated receptors: Potential for modulation of inflammatory disease. Immunobiology, 215(8), 611-616.

Obata, H., Ito, N., Sasaki, M., Saito, S., Goto, F. (2007). Possible involvement of spinal noradrenergic mechanisms in the antiallodynic effect of intrathecally administered 5-HT2c receptor agonists in the rats with peripheral nerve injury. European Journal of Pharmacology, 567(1-2), 89-94.

Obata, H., Saito, S., Sakurazawa, S., Sasaki, M., Usui, T., Goto, F. (2004). Antiallodynic effects of intrathecally administered 5-HT(2c) receptor agonists in rats with nerve injury. Pain, 108(1-2), 163-169.

Odeh, F., Antal, M. (2001). The projections of the midbrain periaqueductal grey to the pons and medulla oblongata in rats. European Journal of Neuroscience, 14(8), 1275-1286.

Ohnishi, K., Nakahata, E., Irie, K., Murakami, A. (2013). Zerumbone, an electrophilic sesquiterpene, induces cellular proteo-stress leading to activation of ubiquitin-proteasome system and autophagy. Biochemical and Biophysical Research Communications, 430(2), 616-622.

Ossipov, M. H., Dussor, G. O., Porreca, F. (2010). Central modulation of pain. The Journal of Clinical Investigation, 120(11), 3779.

Park, S. W., Yi, J. H., Miranpuri, G., Satriotomo, I., Bowen, K., Resnick, D. K., Vemuganti, R. (2007). Thiazolidinedione class of peroxisome

proliferator-activated receptor gamma agonists prevents neuronal damage, motor dysfunction, myelin loss, neuropathic pain, and inflammation after spinal cord injury in adult rats. Journal of Pharmacology and Experimental Therapeutics, 320(3), 1002-1012.

Pascual, D., Goicoechea, C., Suardiaz, M., □ Martin, M. I. (2005). A cannabinoid agonist, win 55,212-2, reduces neuropathic nociception induced by paclitaxel in rats. Pain, 118(1-2), 23-34.

Pasero, C. (2004). Pathophysiology of neuropathic pain. Pain Management Nursing, 5, 3-8.

Pasero, C., Paice, J. A., □ McCaffery, M. (1999). Basic mechanisms underlying the causes and effects of pain (2nd ed.). St. Louis: Mosby.

Patel, R., Goncalves, L., Newman, R., Jiang, F. L., Goldby, A., Reeve, J., Hendrick, A., Teall, M., Hannah, D., Almond, S., Brice, N., □ Dickenson, A. H. (2014). Novel TRPM8 antagonist attenuates cold hypersensitivity after peripheral nerve injury in rats. Journal of Pharmacology and Experimental Therapeutics, 349(1), 47-55.

Paul, D., Yao, D., Zhu, P., Minor, L. D., □ Garcia, M. M. (2001). 5-hydroxytryptamine3 (5-HT3) receptors mediate spinal 5-ht antinociception: An antisense approach. Journal of Pharmacology and Experimental Therapeutics, 298(2), 674-678.

Peng, B., Lin, J.-Y., Shang, Y., Yang, Z.-W., □ Wang, Y.-P. (2010). Plasticity in the synaptic number associated with neuropathic pain in the rat spinal dorsal horn: A stereological study. Neuroscience Letters, 486(1), 24-28.

Perimal, E. K., Akhtar, M. N., Mohamad, A. S., Khalid, M. H., Ming, O. H., Khalid, S., Tatt, L. M., 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(3), 155-162.

Perl, E. R. (2011). Pain and nociception Comprehensive physiology: John Wiley □ Sons, Inc.

Perry, L. M., □ Metzger, J. (1980). Medicinal plants of east and southeast asia: Attributed properties and uses: MIT press, Cambridge.

Pertovaara, A. (2006). Noradrenergic pain modulation. Progress in Neurobiology, 80(2), 53-83.

Pertovaara, A. (2013). The noradrenergic pain regulation system: A potential target for pain therapy. European Journal of Pharmacology, 716(1-3), 2-7.

Pertovaara, A., Auppila, T., Jyv□sj□rvi, E., □ Kalso, E. (1991). Involvement of supraspinal and spinal segmental alpha-2-adrenergic mechanisms in the medetomidine-induced antinociception. Neuroscience, 44(3), 705-714.

Pitcher, M. H., Ribeiro-da-Silva, A., □ Coderre, T. J. (2007). Effects of inflammation on the ultrastructural localization of spinal cord dorsal horn group I metabotropic glutamate receptors. Journal of Comparative Neurology, 505(4), 412-423.

Ploghaus, A., Narain, C., Beckmann, C. F., Clare, S., Bantick, S., Wise, R., Matthews, P. M., Rawlins, J. N. P., □ Tracey, I. (2001). Exacerbation of pain by anxiety is associated with activity in a hippocampal network. Journal of Neuroscience, 21(24), 9896-9903.

Poree, L. R., Guo, T. Z., Kingery, W. S., □ Maze, M. (1998). The analgesic potency of dexmedetomidine is enhanced after nerve injury: A possible role for peripheral alpha2-adrenoceptors. Anesthesia □ Analgesia, 87(4), 941-948.

Posso, I. d. P., Palmeira, C. C. d. A., □ Vieira, □. B. d. M. (2016). Epidemiology of neuropathic pain. Revista Dor, 17, 11-14.

Price, D., Hayashi, H., Dubner, R., □ Ruda, M. (1979). Functional relationships between neurons of marginal and substantia gelatinosa layers of primate dorsal horn. Journal of Neurophysiology, 42(6), 1590-1608.

Proudfit, H., □ Clark, F. (1991). The projections of locus coeruleus neurons to the spinal cord. Progress in Brain Research, 88, 123-141.

Proudfoot, C. J., Garry, E. M., Cottrell, D. F., Rosie, R., Anderson, H., Robertson, D. C., Fleetwood-Walker, S. M., □ Mitchell, R. (2006). Analgesia mediated by the TRPM8 cold receptor in chronic neuropathic pain. Current Biology, 16(16), 1591-1605.

Proudlock, F., Spike, R. C., □ Todd, A. J. (1993). Immunocytochemical study of somatostatin, neurotensin, GABA, and glycine in rat spinal dorsal horn. Journal of Comparative Neurology, 327(2), 289-297.

Pytliak, M., Vargova, V., Mechirova, V., □ Felsoci, M. (2011). Serotonin receptors - from molecular biology to clinical applications. Physiological Research, 60(1), 15-25.

□ian, J., Brown, S. D., □ Carlton, S. M. (1996). Systemic ketamine attenuates nociceptive behaviors in a rat model of peripheral neuropathy. Brain Research, 715(1-2), 51-62.

□uintans, J. S., Antoniolli, A. R., Almeida, J. R., Santana-Filho, V. J., □ □uintans-Junior, L. J. (2014). Natural products evaluated in neuropathic pain

models - a systematic review. Basic Clinical Pharmacology Toxicology, 114(6), 442-450.

Rahman, H. S., Rasedee, A., Othman, H. H., Chartrand, M. S., Namvar, F., Yeap, S. K., Abdul Samad, N., Andas, R. J., Muhammad Nadzri, N., Anasamy, T., Ng, K. B., How, C. W. (2014). Acute toxicity study of zerumbone-loaded nanostructured lipid carrier on balb c mice model. BioMed Research International, 2014, 15.

Rahman, W., Bannister, K., Bee, L. A., Dickenson, A. H. (2011). A pronociceptive role for the 5-HT2 receptor on spinal nociceptive transmission: An in vivo electrophysiological study in the rat. Brain Research, 1382, 29-36.

Rahn, E. J., Hohmann, A. G. (2009). Cannabinoids as pharmacotherapies for neuropathic pain: From the bench to the bedside. Neurotherapeutics, 6(4), 713-737.

Rahn, E. J., Zvonok, A. M., Thakur, G. A., Khanolkar, A. D., Makriyannis, A., Hohmann, A. G. (2008). Selective activation of cannabinoid CB2 receptors suppresses neuropathic nociception induced by treatment with the chemotherapeutic agent paclitaxel in rats. Journal of Pharmacology and Experimental Therapeutics, 327(2), 584-591.

Ramer, M. S., Bisby, M. A. (1997). Rapid sprouting of sympathetic axons in dorsal root ganglia of rats with a chronic constriction injury. Pain, 70(2-3), 237-244.

Rana, V. S., Verdeguer, M., Blazquez, M. A. (2012). Chemical composition of the essential oil of Zingiber zerumbet var. Darcyi. Natural Product Communications, 7(10), 1369-1370.

Rasmussen, P. V., Sindrup, S. H., Jensen, T. S., Bach, F. W. (2004). Symptoms and signs in patients with suspected neuropathic pain. Pain, 110(1), 461-469.

Ray, A. L. (2013). Neuroplasticity, sensitization, and pain. In R. T. Deer, S. M. Leong, A. Buvanendran, V. Gordin, S. P. Kim, J. S. Panchal, L. A. Ray (Eds.), Comprehensive treatment of chronic pain by medical, interventional, and integrative approaches: The American Academy of pain medicine textbook on patient management (pp. 759-768). New York, NY: Springer New York.

Raymond, J. R., Mukhin, Y. V., Gelasco, A., Turner, J., Collinsworth, G., Gettys, T. W., Grewal, J. S., Garnovskaya, M. N. (2001). Multiplicity of mechanisms of serotonin receptor signal transduction. Pharmacology Therapeutics, 92(2-3), 179-212.

Remick, J., Weintraub, H., Setton, R., Offenbacher, J., Fisher, E., □ Schwartzbard, A. (2008). Fibrate therapy: An update. Cardiology in Review, 16(3), 129-141.

R□thelyi, M. (1981). The modular construction of the neuropil in the substantia gelatinosa of the cat□s spinal cord. A computer aided analysis of golgi specimens. Acta morphologica Academiae Scientiarum Hungaricae, 29(1), 1-18.

Reynolds, D. V. (1969). Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science, 164(3878), 444-445.

Riad, M., Garcia, S., Watkins, K. C., Jodoin, N., Doucet, □., Langlois, X., El Mestikawy, S., Hamon, M., □ Descarries, L. (2000). Somatodendritic localization of 5-ht1a and preterminal axonal localization of 5-HT1b serotonin receptors in adult rat brain. Journal of Comparative Neurology, 417(2), 181-194.

Ricote, M., Huang, J. T., Welch, J. S., □ Glass, C. K. (1999). The peroxisome proliferator-activated receptor(PPARgamma) as a regulator of monocyte□macrophage function. Journal of Leukocyte Biology, 66(5), 733-739.

Ricote, M., Li, A. C., Willson, T. M., Kelly, C. J., □ Glass, C. K. (1998). The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature, 391(6662), 79-82.

Ro, L., □ Chang, K. (2005). Neuropathic pain: Mechanisms and treatments. Chang Gung Medical Journal, 28(9), 597.

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(2), 125-129.

Rocha-Gonzalez, H. I., Meneses, A., Carlton, S. M., □ Granados-Soto, V. (2005). Pronociceptive role of peripheral and spinal 5-HT7 receptors in the formalin test. Pain, 117(1-2), 182-192.

Rog, D. J., Nurmikko, T. J., □ Young, C. A. (2007). Oromucosal delta9-tetrahydrocannabinol□cannabidiol for neuropathic pain associated with multiple sclerosis: An uncontrolled, open-label, 2-year extension trial. Clinical Therapeutics, 29(9), 2068-2079.

Rojas-Corrales, M. O., Ortega-Alvaro, A., Gibert-Rahola, J., Roca-Vinardell, A., □ Mico, J. A. (2000). Pindolol, a beta-adrenoceptor blocker□5-hydroxytryptamine(1a□1b) antagonist, enhances the analgesic effect of tramadol. Pain, 88(2), 119-124.

Romero-Sandoval, E. A., McCall, C., □ Eisenach, J. C. (2005). A2-adrenoceptor stimulation transforms immune responses in neuritis and blocks neuritis-induced pain. Journal of Neuroscience, 25(39), 8988-8994.

Rowbotham, M. C., □ Fields, H. L. (1996). The relationship of pain, allodynia and thermal sensation in post-herpetic neuralgia. Brain, 119 (Pt 2), 347-354.

Rowbotham, M. C., Yosipovitch, G., Connolly, M. K., Finlay, D., Forde, G., □ Fields, H. L. (1996). Cutaneous innervation density in the allodynic form of postherpetic neuralgia. Neurobiology of Disease, 3(3), 205-214.

Ruffolo, R. R., Jr., □ Hieble, J. P. (1994). Alpha-adrenoceptors. Pharmacology □ Therapeutics, 61(1-2), 1-64.

Ruffolo, R. R., Jr., Nichols, A. J., Stadel, J. M., □ Hieble, J. P. (1991). Structure and function of alpha-adrenoceptors. Pharmacological Reviews, 43(4), 475-505.

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(3), 1183-1191.

Russo, E. B., Jiang, H.-E., Li, X., Sutton, A., Carboni, A., Del Bianco, F., Mandolino, G., Potter, D. J., Zhao, Y.-X., □ Bera, S. (2008). Phytochemical and genetic analyses of ancient cannabis from central asia. Journal of Experimental Botany, 59(15), 4171-4182.

Russo, R., LoVerme, J., La Rana, G., D□Agostino, G., Sasso, O., Calignano, A., □ Piomelli, D. (2007). Synergistic antinociception by the cannabinoid receptor agonist anandamide and the PPAR-alpha receptor agonist GW7647. European Journal of Pharmacology, 566(1-3), 117-119.

Sacerdote, P., Franchi, S., Moretti, S., Castelli, M., Procacci, P., Magnaghi, V., □ Panerai, A. E. (2013). Cytokine modulation is necessary for efficacious treatment of experimental neuropathic pain. Journal of Neuroimmune Pharmacology, 8(1), 202-211.

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(2), 210-213.

Sadosky, A., McDermott, A. M., Brandenburg, N. A., □ Strauss, M. (2008). A review of the epidemiology of painful diabetic peripheral neuropathy, postherpetic neuralgia, and less commonly studied neuropathic pain conditions. Pain Practice, 8(1), 45-56.

Safayhi, H., Sailer, E.-R. (1997). Anti-inflammatory actions of pentacyclic triterpenes. Planta Medica, 63(06), 487-493.

Sagen, J., Proudfit, H. K. (1981). Hypoalgesia induced by blockade of noradrenergic projections to the raphe magnus: Reversal by blockade of noradrenergic projections to the spinal cord. Brain Research, 223(2), 391-396.

Salt, T. (2001). Metabotropic glutamate (mglu) receptors and nociceptive processing. Drug Development Research, 54(3), 129-139.

Sambasevam, Y., Omar Farouk, A. A., Tengku Mohamad, T. A., Sulaiman, M. R., Bharatham, B. H., Perimal, E. K. (2017). Cardamonin attenuates hyperalgesia and allodynia in a mouse model of chronic constriction injury-induced neuropathic pain: Possible involvement of the opioid system. European Journal of Pharmacology, 796, 32-38.

Sandkuhler, J. (2009). Models and mechanisms of hyperalgesia and allodynia. Physiological Reviews, 89(2), 707-758.

Sandrini, M., Pini, L. A., Vitale, G. (2003). Differential involvement of central 5-HT1b and 5-HT3 receptor subtypes in the antinociceptive effect of paracetamol. Inflammation Research, 52(8), 347-352.

Santos, A. R., Gadotti, V. M., Oliveira, G. L., Tibola, D., Paszcuk, A. F., Neto, A., Spindola, H. M., Souza, M. M., Rodrigues, A. L. S., Calixto, J. B. (2005). Mechanisms involved in the antinociception caused by agmatine in mice. Neuropharmacology, 48(7), 1021-1034.

Schaible, H.-G. (2006). Peripheral and central mechanisms of pain generation Analgesia (pp. 3-28): Springer.

Scheinin, M., Lomasney, J. W., Hayden-Hixson, D. M., Schambra, U. B., Caron, M. G., Lefkowitz, R. J., Fremeau, R. T., Jr. (1994). Distribution of alpha 2-adrenergic receptor subtype gene expression in rat brain. Molecular Brain Research, 21(1-2), 133-149.

Schlereth, T., Birklein, F. (2008). The sympathetic nervous system and pain. NeuroMolecular Medicine, 10(3), 141-147.

Schoenen, J., Van Hees, J., Gybels, J., de Castro Costa, M., Vanderhaeghen, J. J. (1985). Histochemical changes of substance P, FRAP, serotonin and succinic dehydrogenase in the spinal cord of rats with adjuvant arthritis. Life Sciences, 36(13), 1247-1254.

Scott, D. A., Wright, C. E., Angus, J. A. (2004). Evidence that CB-1 and CB-2 cannabinoid receptors mediate antinociception in neuropathic pain in the rat. Pain, 109(1-2), 124-131.

Seifert, F., Kiefer, G., DeCol, R., Schmelz, M., □ Maihofner, C. (2009). Differential endogenous pain modulation in complex-regional pain syndrome. Brain, 132(Pt 3), 788-800.

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(2), 205-218.

Semenchuk, M. R., □ Sherman, S. (2000). Effectiveness of tizanidine in neuropathic pain: An open-label study. The Journal of Pain, 1(4), 285-292.

Serhan, C. N., Chiang, N., □ Van Dyke, T. E. (2008). Resolving inflammation: Dual anti-inflammatory and pro-resolution lipid mediators. Nature Reviews Immunology, 8(5), 349-361.

Serturner, F. (1817). Ueber das morphium, eine neue salifahige grundlage, und die mekonsaure als hauptbestandtheile des opiums. Annalen der Physik, 25, 56-89.

Seyrek, M., Kahraman, S., Deveci, M. S., Yesilyurt, O., □ Dogrul, A. (2010). Systemic cannabinoids produce CB(1)-mediated antinociception by activation of descending serotonergic pathways that act upon spinal 5-HT(7) and 5-HT(2a) receptors. European Journal of Pharmacology, 649(1-3), 183-194.

Sharma, S., Kulkarni, S. K., Agrewala, J. N., □ Chopra, K. (2006). Curcumin attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. European Journal of Pharmacology, 536(3), 256-261.

Sheen, K., □ Chung, J. M. (1993). Signs of neuropathic pain depend on signals from injured nerve fibers in a rat model. Brain Research, 610(1), 62-68.

Sheng-Ji, P. (2001). Ethnobotanical approaches of traditional medicine studies: Some experiences from asia. Pharmaceutical Biology, 39(sup1), 74-79.

Shiojiri, T., Wada, K., Nakajima, A., Katayama, K., Shibuya, A., Kudo, C., Kadowaki, T., Mayumi, T., Yura, Y., □ Kamisaki, Y. (2002). PPARγ ligands inhibit nitrotyrosine formation and inflammatory mediator expressions in adjuvant-induced rheumatoid arthritis mice. European Journal of Pharmacology, 448(2), 231-238.

Shyanti, R. K., Sehrawat, A., Singh, S. V., Mishra, J. P. N., □ Singh, R. P. (2017). Zerumbone modulates cd1d expression and lipid antigen presentation pathway in breast cancer cells. Toxicology in Vitro, 44, 74-84.

Silva, M., Martins, D., Charrua, A., Piscitelli, F., Tavares, I., Morgado, C., □ Di Marzo, V. (2016). Endovanilloid control of pain modulation by the

rostroventromedial medulla in an animal model of diabetic neuropathy. Neuropharmacology, 107, 49-57.

Silveira, J. W., Dias, □. M., Del Bel, E. A., □ Prado, W. A. (2010). Serotonin receptors are involved in the spinal mediation of descending facilitation of surgical incision-induced increase of fos-like immunoreactivity in rats. Molecular Pain, 6, 17.

Sima, A. A. (1980). Peripheral neuropathy in the spontaneously diabetic bb-wistar-rat. An ultrastructural study. Acta Neuropathologica, 51(3), 223-227.

Smith, E. S., □ Lewin, G. R. (2009). Nociceptors: A phylogenetic view. Journal of Comparative Physiology A, 195(12), 1089-1106.

Smith, H. S. (2005). Beta blockers as analgesic adjuvants. Journal of Neuropathic Pain □ Symptom Palliation, 1(4), 21-24.

Smith, T. E., □ Chong, M. S. (2000). Neuropathic pain. Hospital Medicine, 61(11), 760-766.

Sommer, C. (2004). Serotonin in pain and analgesia: Actions in the periphery. Molecular Neurobiology, 30(2), 117-125.

Sommer, C., □ Kress, M. (2004). Recent findings on how proinflammatory cytokines cause pain: Peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neuroscience Letters, 361(1-3), 184-187.

Sorkin, L. S. (1993). NMDA evokes an L-NAME sensitive spinal release of glutamate and citrulline. Neuroreport, 4(5), 479-482.

Sprouse, J. S., □ Aghajanian, G. K. (1987). Electrophysiological responses of serotoninergic dorsal raphe neurons to 5-HT1a and 5-HT1b agonists. Synapse, 1(1), 3-9.

Starowicz, K., □ Przewlocka, B. (2012). Modulation of neuropathic-pain-related behaviour by the spinal endocannabinoid□endovanilloid system. Philosophical Transactions of the Royal Society B: Biological Sciences, 367(1607), 3286-3299.

Stewart, W., □ Maxwell, D. J. (2000). Morphological evidence for selective modulation by serotonin of a subpopulation of dorsal horn cells which possess the neurokinin-1 receptor. European Journal of Neuroscience, 12(12), 4583-4588.

Stubhaug, A., □ Breivik, H. (1997). Longterm treatment of chronic neuropathic pain with the NMDA (n-methyl-d-aspartate) receptor antagonist ketamine. Acta Anaesthesiologica Scandinavica, 41(3), 329-331.

Su, L., Wang, C., Yu, Y.-h., Ren, Y.-y., Xie, K.-l., Wang, G.-l. (2011). Role of TRPM8 in dorsal root ganglion in nerve injury-induced chronic pain. BMC Neuroscience, 12(1), 120.

Sugiura, T., Kondo, S., Sukagawa, A., Nakane, S., Shinoda, A., Itoh, K., Yamashita, A., Waku, K. (1995). 2-arachidonoylglycerol: A possible endogenous cannabinoid receptor ligand in brain. Biochemical and Biophysical Research Communications, 215(1), 89-97.

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. (2010a). Anti-inflammatory effect of zerumbone on acute and chronic inflammation models in mice. Fitoterapia, 81(7), 855-858.

Sulaiman, M. R., Perimal, E. K., Zakaria, Z. A., Mokhtar, F., Akhtar, M. N., Lajis, N. H., Israf, D. A. (2009). Preliminary analysis of the antinociceptive activity of zerumbone. Fitoterapia, 80(4), 230-232.

Sulaiman, M. R., Tengku Mohamad, T. A., Shaik Mossadeq, W. M., Moin, S., Yusof, M., Mokhtar, A. F., Zakaria, Z. A., Israf, D. A., Lajis, N. (2010b). Antinociceptive activity of the essential oil of Zingiber zerumbet. Planta Medica, 76(02), 107-112.

Suzuki, R., Matthews, E. A., Dickenson, A. H. (2001). Comparison of the effects of mk-801, ketamine and memantine on responses of spinal dorsal horn neurones in a rat model of mononeuropathy. Pain, 91(1-2), 101-109.

Swaynok, J. (1989). The role of ascending and descending nor-adrenergic and serotonergic pathways in opioid and non-opioid antinociception as revealed by lesion studies. Canadian Journal of Physiology and Pharmacology, 67, 975-988.

Swieboda, P., Filip, R., Prystupa, A., Drozd, M. (2013). Assessment of pain: Types, mechanism and treatment. Annals of Agricultural and Environmental Medicine, Spec no. 1, 2-7.

Takada, Y., Murakami, A., Aggarwal, B. B. (2005). Zerumbone abolishes nf-kappab and ikappabalpha kinase activation leading to suppression of antiapoptotic and metastatic gene expression, upregulation of apoptosis, and downregulation of invasion. Oncogene, 24(46), 6957-6969.

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(4), 380-384.

Takeshita, N., □ Yamaguchi, I. (1995). Meta-chlorophenylpiperazine attenuates formalin-induced nociceptive responses through 5-HT1□2 receptors in both normal and diabetic mice. British Journal of Pharmacology, 116(8), 3133-3138.

Tanabe, M., Takasu, K., Kasuya, N., Shimizu, S., Honda, M., □ Ono, H. (2005). Role of descending noradrenergic system and spinal α2-adrenergic receptors in the effects of gabapentin on thermal and mechanical nociception after partial nerve injury in the mouse. British Journal of Pharmacology, 144(5), 703-714.

Tanabe, M., Tokuda, Y., Takasu, K., Ono, K., Honda, M., □ Ono, H. (2007). The synthetic TRH analogue taltirelin exerts modality-specific antinociceptive effects via distinct descending monoaminergic systems. British Journal of Pharmacology, 150(4), 403-414.

Tang, W., Zeve, D., Seo, J., Jo, A. Y., □ Graff, J. M. (2011). Thiazolidinediones regulate adipose lineage dynamics. Cell Metabolism, 14(1), 116-122.

Tang, Y.-P., Shimizu, E., Dube, G. R., Rampon, C., Kerchner, G. A., Zhuo, M., Liu, G., □ Tsien, J. Z. (1999). Genetic enhancement of learning and memory in mice. Nature, 401(6748), 63-69.

Tank, A. W., □ Lee Wong, D. (2015). Peripheral and central effects of circulating catecholamines. Comprehensive Physiology, 5(1), 1-15.

Taylor, B., Kriedt, C., Nagalingam, S., Dadia, N., □ Badr, M. (2005). Central administration of perfluorooctanoic acid inhibits cutaneous inflammation. Inflammation Research, 54(6), 235-242.

Taylor, B. K., Dadia, N., Yang, C. B., Krishnan, S., □ Badr, M. (2002). Peroxisome proliferator-activated receptor agonists inhibit inflammatory edema and hyperalgesia. Inflammation, 26(3), 121-127.

Teasell, R. W., □ Arnold, J. M. O. (2004). Alpha-1 adrenoceptor hyperresponsiveness in three neuropathic pain states: Complex regional pain syndrome 1, diabetic peripheral neuropathic pain and central pain states following spinal cord injury. Pain Research and Management, 9(2), 89-97.

Thacker, M. A., Clark, A. K., Marchand, F., □ McMahon, S. B. (2007). Pathophysiology of peripheral neuropathic pain: Immune cells and molecules. Anesthesia □ Analgesia, 105(3), 838-847.

Thibault, K., Van Steenwinckel, J., Brisorgueil, M. J., Fischer, J., Hamon, M., Calvino, B., □ Conrath, M. (2008). Serotonin 5-HT2a receptor involvement and fos expression at the spinal level in vincristine-induced neuropathy in the rat. Pain, 140(2), 305-322.

T□lle, T. R. (2010). Challenges with current treatment of neuropathic pain. European Journal of Pain Supplements, 4(S2), 161-165.

Tontonoz, P., □ Spiegelman, B. M. (2008). Fat and beyond: The diverse biology of PPARgamma. Annual Review of Biochemistry, 77, 289-312.

Tracey, I., □ Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. Neuron, 55(3), 377-391.

Tyce, G., □ Yaksh, T. (1981). Monoamine release from cat spinal cord by somatic stimuli: An intrinsic modulatory system. The Journal of Physiology, 314(1), 513-529.

Ulugol, A., Oltulu, C., Gunduz, O., Citak, C., Carrara, R., Shaqaqi, M. R., Sanchez, A. M., □ Dogrul, A. (2012). 5-HT7 receptor activation attenuates thermal hyperalgesia in streptozocin-induced diabetic mice. Pharmacology Biochemistry and Behavior, 102(2), 344-348.

Urban, L., Thompson, S. W., □ Dray, A. (1994). Modulation of spinal excitability: Co-operation between neurokinin and excitatory amino acid neurotransmitters. Trends in Neurosciences, 17(10), 432-438.

Valverderk, O., Mico, J. A., Maldonado, R., Mellado, M., □ Gibert-Rahola, J. (1994). Participation of opioid and monoaminergic mechanisms on the antinociceptive effect induced by tricyclic antidepressants in two behavioural pain tests in mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 18(6), 1073-1092.

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(4), 654-662.

Van Steenwinckel, J., Brisorgueil, M. J., Fischer, J., Verge, D., Gingrich, J. A., Bourgoin, S., Hamon, M., Bernard, R., □ Conrath, M. (2008). Role of spinal serotonin 5-HT2a receptor in 2□,3□-dideoxycytidine-induced neuropathic pain in the rat and the mouse. Pain, 137(1), 66-80.

Vanderah, T. W., Laughlin, T., Lashbrook, J. M., Nichols, M. L., Wilcox, G. L., Ossipov, M. H., Malan, T. P., Jr., □ Porreca, F. (1996). Single intrathecal injections of dynorphin a or des-tyr-dynorphins produce long-lasting allodynia in rats: Blockade by MK-801 but not naloxone. Pain, 68(2-3), 275-281.

Vanegas, H., □ Schaible, H. G. (2004). Descending control of persistent pain: Inhibitory or facilitatory□Brain Research Reviews, 46(3), 295-309.

Vaughan, C. W., Connor, M., Bagley, E. E., □ Christie, M. J. (2000). Actions of cannabinoids on membrane properties and synaptic transmission in rat periaqueductal gray neurons in vitro. Molecular Pharmacology, 57(2), 288-295.

Veldhuis, N. A., Poole, D. P., Grace, M., McIntyre, P., □ Bunnett, N. W. (2015). The G protein□coupled receptor□transient receptor potential channel axis: Molecular insights for targeting disorders of sensation and inflammation. Pharmacological Reviews, 67(1), 36-73.

Vicini, S., Wang, J. F., Li, J. H., Zhu, W. J., Wang, Y. H., Luo, J. H., Wolfe, B. B., □ Grayson, D. R. (1998). Functional and pharmacological differences between recombinant n-methyl-d-aspartate receptors. Journal of Neurophysiology, 79(2), 555-566.

Vignes, M., □ Collingridge, G. L. (1997). The synaptic activation of kainate receptors. Nature, 388(6638), 179-182.

Vinik, E. J., Hayes, R. P., Oglesby, A., Bastyr, E., Barlow, P., Ford-Molvik, S. L., □ Vinik, A. I. (2005). The development and validation of the Norfolk □OL-DN, a new measure of patients□perception of the effects of diabetes and diabetic neuropathy. Diabetes Technology □ Therapeutics, 7(3), 497-508.

Voscopoulos, C., □ Lema, M. (2010). When does acute pain become chronic□ British Journal of Anaesthesia, 105 Suppl 1, i69-85.

Wachter, S. B., □ Gilbert, E. M. (2012). Beta-adrenergic receptors, from their discovery and characterization through their manipulation to beneficial clinical application. Cardiology, 122(2), 104-112.

Waldhoer, M., Bartlett, S. E., □ Whistler, J. L. (2004). Opioid receptors. Annual Review of Biochemistry, 73, 953-990.

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(2), 103-111.

Wang, R., Xu, Y., Wu, H.-L., Li, Y.-B., Li, Y.-H., Guo, J.-B., □ Li, X.-J. (2008). The antidepressant effects of curcumin in the forced swimming test involve 5-HT1 and 5-HT2 receptors. European Journal of Pharmacology, 578(1), 43-50.

Wang, W., Mei, X.-P., Wei, Y.-Y., Zhang, M.-M., Zhang, T., Wang, W., Xu, L.-X., Wu, S.-X., □ Li, Y.-□. (2011). Neuronal NR2B-containing NMDA

receptor mediates spinal astrocytic c-jun n-terminal kinase activation in a rat model of neuropathic pain. Brain, Behavior, and Immunity, 25(7), 1355-1366.

Wang, W., Wu, S.-X., Wang, Y.-Y., Liu, X.-Y., □ Li, Y.-□. (2003). 5-hydroxytryptamine1a receptor is involved in the bee venom induced inflammatory pain. Pain, 106(1-2), 135-142.

Wang, Y., Cao, S. E., Tian, J., Liu, G., Zhang, X., □ Li, P. (2013). Auraptenol attenuates vincristine-induced mechanical hyperalgesia through serotonin 5-HT1a receptors. Scientific Reports, 3, 3377.

Waters, A. J., □ Lumb, B. M. (1997). Inhibitory effects evoked from both the lateral and ventrolateral periaqueductal grey are selective for the nociceptive responses of rat dorsal horn neurones. Brain Research, 752(1-2), 239-249.

Watson, B. D., Prado, R., Dietrich, W. D., Ginsberg, M. D., □ Green, B. A. (1986). Photochemically induced spinal cord injury in the rat. Brain Research, 367(1-2), 296-300.

Wei, F., □iu, C.-S., Kim, S. J., Muglia, L., Maas, J. W., Pineda, V. V., Xu, H.-M., Chen, Z.-F., Storm, D. R., □ Muglia, L. J. (2002). Genetic elimination of behavioral sensitization in mice lacking calmodulin-stimulated adenylyl cyclases. Neuron, 36(4), 713-726.

Wei, H., Hamalainen, M. M., Saarnilehto, M., Koivisto, A., □ Pertovaara, A. (2009). Attenuation of mechanical hypersensitivity by an antagonist of the TRPA1 ion channel in diabetic animals. Anesthesiology, 111(1), 147-154.

Weissmann-Nanopoulos, D., Mach, E., Magre, J., Demassey, Y., □ Pujol, J.-F. (1985). Evidence for the localization of 5ht1a binding sites on serotonin containing neurons in the raphe dorsalis and raphe centralis nuclei of the rat brain. Neurochemistry International, 7(6), 1061-1072.

Wilcox, G. L. (1988). Pharmacological studies of grooming and scratching behavior elicited by spinal substance p and excitatory amino acids. Annals of the New York Academy of Sciences, 525, 228-236.

Wilder-Smith, C. H. (2011). The balancing act: Endogenous modulation of pain in functional gastrointestinal disorders. Gut, 60(11), 1589-1599.

Willis, W. D. (2004). Sensory mechanisms of the spinal cord (3rd ed.). New York: Kluwer Academic□Plenum Publishers.

Willson, T. M., Lambert, M. H., □ Kliewer, S. A. (2001). Peroxisome proliferator□ activated receptor γ and metabolic disease. Annual Review of Biochemistry, 70(1), 341-367.

Wilson-Gerwing, T. D., Dmyterko, M. V., Zochodne, D. W., Johnston, J. M., Verge, V. M. (2005). Neurotrophin-3 suppresses thermal hyperalgesia associated with neuropathic pain and attenuates transient receptor potential vanilloid receptor-1 expression in adult sensory neurons. Journal of Neuroscience, 25(3), 758-767.

Woolf, C. J. (1995). An overview of the mechanisms of hyperalgesia. Pulmonary Pharmacology and Therapeutics, 8(4-5), 161-167.

Woolf, C. J., American College of, P., American Physiological, S. (2004). Pain: Moving from symptom control toward mechanism-specific pharmacologic management. Annals of Internal Medicine, 140(6), 441-451.

Woolf, C. J., Doubell, T. P. (1994). The pathophysiology of chronic pain--increased sensitivity to low threshold a beta-fibre inputs. Current Opinion in Neurobiology, 4(4), 525-534.

Woolf, C. J., Ma, . (2007). Nociceptors--noxious stimulus detectors. Neuron, 55(3), 353-364.

Woolf, C. J., Mannion, R. J. (1999). Neuropathic pain: Aetiology, symptoms, mechanisms, and management. Lancet, 353(9168), 1959-1964.

Woolf, C. J., Salter, M. W. (2000). Neuronal plasticity: Increasing the gain in pain. Science, 288(5472), 1765-1769.

Woolf, C. J., Shortland, P., Coggeshall, R. E. (1992). Peripheral nerve injury triggers central sprouting of myelinated afferents. Nature, 355(6355), 75-78.

Wu, G., Ringkamp, M., Hartke, T. V., Murinson, B. B., Campbell, J. N., Griffin, J. W., Meyer, R. A. (2001). Early onset of spontaneous activity in uninjured c-fiber nociceptors after injury to neighboring nerve fibers. Journal of Neuroscience, 21(8), RC140.

Wu, G., Ringkamp, M., Murinson, B. B., Pogatzki, E. M., Hartke, T. V., Weerahandi, H. M., Campbell, J. N., Griffin, J. W., Meyer, R. A. (2002). Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured c-fiber afferents. Journal of Neuroscience, 22(17), 7746-7753.

Wu, L.-J., Toyoda, H., Zhao, M.-G., Lee, Y.-S., Tang, J., Ko, S. W., Jia, Y. H., Shum, F. W., Zerbinatti, C. V., Bu, G. (2005). Upregulation of forebrain NMDA NR2B receptors contributes to behavioral sensitization after inflammation. Journal of Neuroscience, 25(48), 11107-11116.

Wu, Z., Yang, □., Crook, R. J., O□Neil, R. G., □ Walters, E. T. (2013). TRPV1 channels make major contributions to behavioral hypersensitivity and spontaneous activity in nociceptors after spinal cord injury. Pain, 154(10), 2130-2141.

Wuarin-Bierman, L., Zahnd, G. R., Kaufmann, F., Burcklen, L., □ Adler, J. (1987). Hyperalgesia in spontaneous and experimental animal models of diabetic neuropathy. Diabetologia, 30(8), 653-658.

Xia, Z., Dudek, H., Miranti, C. K., □ Greenberg, M. E. (1996). Calcium influx via the NMDA receptor induces immediate early gene transcription by a MAP kinase□ERK-dependent mechanism. Journal of Neuroscience, 16(17), 5425-5436.

Xie, J., Ho Lee, Y., Wang, C., Mo Chung, J., □ Chung, K. (2001). Differential expression of alpha1-adrenoceptor subtype mRNAs in the dorsal root ganglion after spinal nerve ligation. Molecular Brain Research, 93(2), 164-172.

Xu, Y., Lin, D., Yu, X., Xie, X., Wang, L., Lian, L., Fei, N., Chen, J., Zhu, N., Wang, G., Huang, X., □ Pan, J. (2016). The antinociceptive effects of ferulic acid on neuropathic pain: Involvement of descending monoaminergic system and opioid receptors. Oncotarget, 7(15), 20455-20468.

Xu, Y.-□., Jin, S.-J., Liu, N., Li, Y.-X., Zheng, J., Ma, L., Du, J., Zhou, R., Zhao, C.-J., □ Niu, Y. (2014). Aloperine attenuated neuropathic pain induced by chronic constriction injury via anti-oxidation activity and suppression of the nuclear factor kappa b pathway. Biochemical and Biophysical Research Communications, 451(4), 568-573.

Yagi, J., □ Sumino, R. (1998). Inhibition of a hyperpolarization-activated current by clonidine in rat dorsal root ganglion neurons. Journal of Neurophysiology, 80(3), 1094-1104.

Yaksh, T. L., Pogrel, J. W., Lee, Y. W., □ Chaplan, S. R. (1995). Reversal of nerve ligation-induced allodynia by spinal alpha-2 adrenoceptor agonists. Journal of Pharmacology and Experimental Therapeutics, 272(1), 207-214.

Yaksh, T. L., □ Tyce, G. M. (1979). Microinjection of morphine into the periaqueductal gray evokes the release of serotonin from spinal cord. Brain Research, 171(1), 176-181.

Yaksh, T. L., □ Wilson, P. R. (1979). Spinal serotonin terminal system mediates antinociception. Journal of Pharmacology and Experimental Therapeutics, 208(3), 446-453.

Yalcin, I., Choucair-Jaafar, N., Benbouzid, M., Tessier, L. H., Muller, A., Hein, L., Freund-Mercier, M. J., Barrot, M. (2009a). B2-adrenoceptors are critical for antidepressant treatment of neuropathic pain. Annals of Neurology, 65(2), 218-225.

Yalcin, I., Tessier, L.-H., Petit-Demouli re, N., Doridot, S., Hein, L., Freund-Mercier, M.-J., Barrot, M. (2009b). B 2-adrenoceptors are essential for desipramine, venlafaxine or reboxetine action in neuropathic pain. Neurobiology of Disease, 33(3), 386-394.

Yamamoto, W., Sugiura, A., Nakazato-Imasato, E., Kita, Y. (2008). Characterization of primary sensory neurons mediating static and dynamic allodynia in rat chronic constriction injury model. Journal of Pharmacy and Pharmacology, 60(6), 717-722.

Yan, H., Ren, M. Y., Wang, Z. X., Feng, S. J., Li, S., Cheng, Y., Hu, C. X., Gao, S. ., Zhang, G. . (2017). Zerumbone inhibits melanoma cell proliferation and migration by altering mitochondrial functions. Oncology Letters, 13(4), 2397-2402.

Yan, . S., Yan, S. E. (2001). Serotonin-1b receptor-mediated inhibition of 3h GABA release from rat ventral tegmental area slices. Journal of Neurochemistry, 79(4), 914-922.

Yanarates, O., Dogrul, A., Yildirim, V., Sahin, A., Sizlan, A., Seyrek, M., Akgul, O., Kozak, O., Kurt, E., Aypar, U. (2010). Spinal 5-HT7 receptors play an important role in the antinociceptive and antihyperalgesic effects of tramadol and its metabolite, o-desmethyltramadol, via activation of descending serotonergic pathways. Anesthesiology, 112(3), 696-710.

Yeomans, D., Proudfit, H. (1990). Projections of substance p-immunoreactive neurons located in the ventromedial medulla to the a7 noradrenergic nucleus of the rat demonstrated using retrograde tracing combined with immunocytochemistry. Brain Research, 532(1), 329-332.

Yeung, J. C., Yaksh, T. L., Rudy, T. A. (1977). Concurrent mapping of brain sites for sensitivity to the direct application of morphine and focal electrical stimulation in the production of antinociception in the rat. Pain, 4(1), 23-40.

Yezierski, R. P., Park, S. H. (1993). The mechanosensitivity of spinal sensory neurons following intraspinal injections of quisqualic acid in the rat. Neuroscience Letters, 157(1), 115-119.

Yi, J.-H., Park, S.-W., Brooks, N., Lang, B. T., Vemuganti, R. (2008). PPARγ agonist rosiglitazone is neuroprotective after traumatic brain injury via anti-inflammatory and anti-oxidative mechanisms. Brain Research, 1244, 164-172.

Yob, N. J., Jofrry, S. M., Affandi, 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, 2011, 543216.

Yogeeswari, P., Semwal, A., Mishra, R., □ Sriram, D. (2009). Current approaches with the glutamatergic system as targets in the treatment of neuropathic pain. Expert Opinion on Therapeutic Targets, 13(8), 925-943.

Yoon, Y. W., Na, H. S., □ Chung, J. M. (1996). Contributions of injured and intact afferents to neuropathic pain in an experimental rat model. Pain, 64(1), 27-36.

Yu, X. H., Cao, C. □., Martino, G., Puma, C., Morinville, A., St-Onge, S., Lessard, □., Perkins, M. N., □ Laird, J. M. (2010). A peripherally restricted cannabinoid receptor agonist produces robust anti-nociceptive effects in rodent models of inflammatory and neuropathic pain. PAIN□, 151(2), 337-344.

Zeilhofer, H. U. (2005). Synaptic modulation in pain pathways. Reviews of Physiology, Biochemistry and Pharmacology, 154, 73-100.

Zelenka, M., Schafers, M., □ Sommer, C. (2005). Intraneural injection of interleukin-1beta and tumor necrosis factor-alpha into rat sciatic nerve at physiological doses induces signs of neuropathic pain. Pain, 116(3), 257-263.

Zhang, C., Yang, S. W., Guo, Y. G., □iao, J. T., □ Dafny, N. (1997). Locus coeruleus stimulation modulates the nociceptive response in parafascicular neurons: An analysis of descending and ascending pathways. Brain Research Bulletin, 42(4), 273-278.

Zhang, J., Huang, X.-Y., Ye, M.-L., Luo, C.-X., Wu, H.-Y., Hu, Y., Zhou, □.-G., Wu, D.-L., Zhu, L.-J., □ Zhu, D.-Y. (2010). Neuronal nitric oxide synthase alteration accounts for the role of 5-HT1a receptor in modulating anxiety-related behaviors. Journal of Neuroscience, 30(7), 2433-2441.

Zhang, Y., Wang, C., Wang, L., Parks, G. S., Zhang, X., Guo, Z., Ke, Y., Li, K. W., Kim, M. K., Vo, B., Borrelli, E., Ge, G., Yang, L., Wang, Z., Garcia-Fuster, M. J., Luo, Z. D., Liang, X., □ Civelli, O. (2014). A novel analgesic isolated from a traditional chinese medicine. Current Biology, 24(2), 117-123.

Zhao, X., Wang, C., Cui, W. G., Ma, □., □ Zhou, W. H. (2015). Fisetin exerts antihyperalgesic effect in a mouse model of neuropathic pain: Engagement of spinal serotonergic system. Scientific Reports, 5, 9043.

Zhao, X., Wang, C., Zhang, J. F., Liu, L., Liu, A. M., Ma, □., Zhou, W. H., □ Xu, Y. (2014). Chronic curcumin treatment normalizes depression-like behaviors in mice with mononeuropathy: Involvement of supraspinal serotonergic system and GABAa receptor. Psychopharmacology, 231(10), 2171-2187.

Zhao, X., Xu, Y., Zhao, □., Chen, C.-R., Liu, A.-M., □ Huang, Z.-L. (2012). Curcumin exerts antinociceptive effects in a mouse model of neuropathic pain: Descending monoamine system and opioid receptors are differentially involved. Neuropharmacology, 62(2), 843-854.

Zhou, X. F., Deng, Y. S., Chie, E., Xue, □., Zhong, J. H., McLachlan, E. M., Rush, R. A., □ Xian, C. J. (1999). Satellite-cell-derived nerve growth factor and neurotrophin-3 are involved in noradrenergic sprouting in the dorsal root ganglia following peripheral nerve injury in the rat. European Journal of Neuroscience, 11(5), 1711-1722.

Zimmermann, M. (1983). Ethical guidelines for investigations of experimental pain in conscious animals. Pain, 16(2), 109-110.

Zlas, J., Stark, H., Seligman, J., Levy, R., Werker, E., Breuer, A., □ Mechoulam, R. (1993). Early medical use of cannabis. Nature, 363(6426), 215-215.

Zuardi, A. W. (2006). History of cannabis as a medicine: A review. Revista Brasileira de Psiquiatr□a, 28(2), 153-157.

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.

Zygmunt, P. M., Petersson, J., Andersson, D. A., Chuang, H., Sorgard, M., Di Marzo, V., Julius, D., □ Hogestatt, E. D. (1999). Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. Nature, 400(6743), 452-457.