We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Capsaicin: Aromatic Basis and Mechanism of Action: An Example of Positive Inhibition

Adebayo Taiwo Ezekiel Jolayemi

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/66103>

Abstract

This work will, in addition to describing the aromatic basis of capsaicin, elucidate its mechanism of action through a positive inhibition of the nerve conduction, which ultimately accounts for the various pharmacological effects of capsaicin on pain control, cardiovascular mechanisms, as well as its effects on genitourinary and gastrointestinal tracts.

Keywords: capsaicin, aromatics, desensitization, mechanism of action, positive inhibition

1. Introduction

The current study is a systemic review of the pharmacology and chemistry of capsaicin and capsaicinoids. The genus *Capsicum* is a member of the Solanaceae family that includes tomato, potato, tobacco, and petunia. The genus *Capsicum* consists of approximately 22 wild species and 5 domesticated species [1] including *C. annuum*, *C. baccatum*, *C. chinense*, *C. frutescens*, and *C. pubescens*.

Capsicum species have been used as medicinal plants to treat intestinal upsets and indigestion and also as stimulants, rubefacient, and tonic. They have also been used as folk remedies for dropsy, colic, diarrhea, asthma, arthritis, muscle cramps, and toothache. In addition, *Capsicum frutescens* L. has been reported to have hypoglycemic properties [2]. However, prolonged contact with the skin may cause dermatitis and blisters, while excessive consumption can cause gastroenteritis and/or kidney damage. Besides, paprika and cayenne pepper may be cytotoxic to mammalian cells, *in vitro*. Moreover, consumption of red pepper may aggravate symptoms

of duodenal ulcers. It has also been shown that high levels of ground hot pepper have induced stomach ulcers and cirrhosis of the liver in laboratory animals. As a stimulant *Capsicum* species could stimulate body temperature, salivation, and increase gastric juices.

This study was undertaken to investigate the anti-inflammatory property of *Capsicum frutescens* ethyl acetate extract (CFE) and capsaicin (CPF) in rat model to provide a pharmacological rationale for the folklore medicine uses of capsaicin and capsaicinoids to treat arthritis, muscle sprain, and other inflammatory conditions in some communities. One of the main objectives of this study was to determine if *Capsicum frutescens* fruit extract in this study has similar efficacy on peripheral and central components of pain as so described for *Capsicum spp.* (Linn) [Solanaceae] from other parts of the world, such as from India, Mexico, Thailand, and South America [3].

2. Research methods

Following Ethics approval by the Animal Ethics Committee of the University of KwaZulu—Natal; Westville Campus, various parallel and comparative studies were carried out on crude extract ethyl acetate of *Capsicum frutescens* and synthetic capsaicin. The studies were to elucidate the analgesic, antiinflammatory, gastro-intestinal effects and the effects on coagulation of both compounds. The discussion that follows is a systemic review of the pharmacological effects of capsaicin. The “hot plate” and “acetic acid” analgesic tests methods were used for central and peripheral nervous system investigations on pain mechanisms, using the mean reaction time and inhibition of writhing, respectively. The effects of *Capsicum*-derived capsaicin on chick isolated parasympathetically innervated esophagus, rabbit duodenum, and guinea pig ileum were investigated in Ugo Basile organ baths, respectively. In all cases, concentration-response curves to standard agonists were investigated in the absence and in the presence of capsaicin (CPE), or standard antagonists. Following 2 weeks of treatment with capsaicin and capsicum extracts, the effects of capsaicin on coagulation was tested. The results of these studies show comparable analgesic to morphine and diclofenac on the peripheral analgesic mechanisms and more intense central analgesia compared to morphine ($p < 0.1$). Besides, capsaicin increased the INR by 1.25 times compared to control ($p < 0.01$) and has a dose-dependent relaxation of the gastro-intestinal smooth muscles ($p < 0.1$).

3. Data analysis

Experimental data obtained were analyzed and presented as means (+SEM). The data from “control” rats were used as baseline values while the mean reaction times to the pain stimulus or the writhing were recorded and subsequently analyzed, using a two-way ANOVA. Interobserver differences were assessed by Wilcoxon and Kruskal-Wallis tests. Student's *t*-test was used to test for the difference between the means when two groups were analyzed. Where the groups are more than two, ANOVA was used to test for differences between the groups.

Statistical significance was by using a double-tailed CI of 95% and a *p*-value of less than 0.05. Pearson correlation coefficient was used to assess the activity of *Capsicum frutescens*-derived capsaicin extract, compared to that of the synthetic capsaicin and to compare results from selected groups.

4. Discussion

Capsicum species occur worldwide, and has been used for more than 9000 years by the Chinese, Indians, and Africans for medicinal and nonmedicinal purposes [4], for example, for pain, among other things. Pain is perceived through both peripheral and central mechanisms. Peripheral mechanisms typically involve the nociceptors, while central mechanisms involve the process of central sensitization. Pain is sensed by nociceptors located in the sensory nerve endings. Messages are relayed through complex multisynaptic afferents to the dorsal column by means of transmission and transduction of chemical messages, which are relayed via the spinal mechanisms and processed for appropriate supranuclear interpretation. Finally, the motor effector organs are facilitated to respond according to the type of pain [5, 6].

The neural impulses, which originate from the nociceptors, relay through the primary afferent nerves (PAN), to the spinal cord, or via the cranial nerves to the brain stem, for those impulses that originate from the head and neck. The cell bodies of these ganglia are located in the dorsal root ganglia, or the respective cell bodies in the cases of cranial nerves V, VIII, IX, and X. By means of complex synapses, messages are relayed to ascending pathways.

There are several biochemical mediators (and neurotransmitters), which are involved in pain transmission and perception. Peripherally, the most important of these amines are the cyclo-oxygenase agonists and the leukotrienes. Others are catecholamines, acetylcholine, vasoactive intestinal polypeptides (VIP), neuropeptides Y (NPY), cholecystokinin, 5-hydroxytryptamine, neurotensin, tachykinin, and bradykinins [7, 8]. The opioid receptors act both centrally and peripherally. In addition, the central cyclo-oxygenase action has been found with acetaminophen [9]. Centrally acting neuromediators can be classified into “excitatory” and “inhibitory” neuromediators. Glutamate and aspartate are the examples of excitatory amino acids acting as neurotransmitters centrally, while substance P (SP), calcitonin gene-related peptide (CGRP) [10], and growth factors (e.g., brain-derived neurotrophic factors) are other examples. Inhibitory neuromediators include endogenous opioids, such as enkephalin and β -endorphins. Others are gamma-aminobutyric acid (GABA), glycine, and β -adrenergic agonists [11]. Conversely, any agent acting on these receptors and neuromediators have the ability to modulate pain. The aberration of inflammatory and neuropathic enhancement of pain perception as seen in allodynia (painful touch) and hyperalgesia are due to increased release of SP from *substantia gelatinosa*. This phenomenon is called “peripheral sensitization.”

The memory of pain, neural plasticity, wide dynamic range activity, and the winding phenomenon are enhanced by *N*-methyl-D-aspartate receptor through an early expression of genetic coding through *c-fos* and *v-fos* oncogenes [12–15]. This neural plasticity leads to the phenomenon of central sensitization as typified by stump and phantom pain. Both

hyperalgesia and allodynia, which are known side effects of capsaicin [16], are results of peripheral and central sensitization. In addition, the repetitive C fiber stimulation produces the winding-up phenomenon.

Injury leads to nociception, transduction, receptor modification, uncoordinated sprouting, and growth of injured axons and ectopic epileptic firing of nerves [17]. Although the hypothalamus receives an enormous amount of stimuli, it is devoid of the ability to discriminate, since it is not somato-topically organized. It is also not able to localize pain. However, discrimination and localization are possible by the third-order neurons connecting to the prefrontal gyrus in the cerebral cortex. This is the basis for the use of secondary analgesia such as antidepressants and anticonvulsants.

The ascending order is not alone in pain modulation. There is enough evidence to suggest that the descending tracts have a role in the modulation of pain [18]. In the late 1960s, it was observed that neurons in the dorsal horn of decerebrated animals are more responsive to painful stimuli when the spinal cord is blocked [19]. Also in the late 1980s, electrical stimulation of the periaqueductal gyrus was found to produce profound relief of pain in animals [17]. These studies provided scientific basis for stimulation-produced analgesia. In addition, further studies showed that instillation of small doses of morphine in the regions such as periaqueductal system (PAG) produced significant analgesia.

Substance P is the active neurotransmitter that is released at the primary nerve endings of primary afferent neurons (PAN). It is usually synthesized at the *substantia gelatinosa* of the dorsal horn. On release from PAN, substance P from the dorsal horn of the spinal cord exhibits systemic actions. For example, the expression of substance P and vanilloid receptor (VR1) were found in the trigeminal sensory neurons projecting from PAN to the nasal mucosa in the mouse [20, 21]. The release of both substance P and neurokinin A (NKA) from PAN to various stimuli induced by capsaicin (vanilloid) receptor (VR1) results in potent proinflammatory effects on the airways [22, 23].

Expression of substance P was found to correlate with the severity of diarrhea in cryptosporidiosis from the result in electrogenic chloride anion secretion [24,25] and found three kinds of current in response to substance P in bullfrog dorsal root ganglion neurons. They are either G-protein coupled channel, slow activating I (SP); or directly opened channel, fast activating I (SP); or both, moderately activating I (SP). All the three were inwardly directed currents with the ionic mechanism underlying slow activating I (SP) deduced as closure of K^+ channels. The fast-activating channel is due to the opening of sodium channels. These correlate with the three subtypes of SP receptor, immunoreactive interneurons described in the rat basolateral amygdala [26]. Furthermore, the secretion of HCO_3^- through secretin was abolished by substance P [15, 24, 27].

Other systems affected by substance P include the cardiovascular system. Low dose systemic administration of substance P caused hypertension and tachycardia, while unilateral or bilateral injections into the rat's *nucleus tractus solitarius* caused slow increase in blood pressure and heart rate, which peaked in 1.5–5 min after injection and lasted for 20–30 min. These effects are vagal mediated [28, 29].

Furthermore, the swellings that typically accompany complex regional pain syndrome have been found to be due to extravasation of substance P-induced protein [24, 30].

Capsaicin is the main pungent ingredient in “hot” chili peppers, and elicits a burning pain by selectively activating sensory neurons that convey information about noxious stimuli to the central nervous system [31, 32]. However, capsaicin-induced ion refluxes increase cyclic GMP and not cyclic AMP [33], capsaicin has selective action on unmyelinated C-fibers and thinly myelinated A primary sensory neurons [33].

Several sensory stimuli including noxious pressure, heat, and chemical irritation could affect capsaicin-sensitive fibers, which are polymodal in nature. These nociceptors are the most abundant class of nociceptive fibers. On stimulation by capsaicin, nociceptive neurons release glutamate, which are a rapidly acting central neurotransmitter and an excitatory amino acid. Likewise, the transient receptor potential (TRP) family of ion channels are activated by a diverse range of stimuli, including heat, protons, lipids, phorbols, phosphorylation, changes in extracellular osmolarity and/or pressure, and depletion of intracellular Ca^{2+} stores. In all, VR 1 remains the only channel activated by vanilloids such as capsaicin [34].

In addition, they also express neuropeptides, such as calcitonin-gene-related-peptide (CGRP), substance P, neurokinin A, and somatostatin, which, on release to the spinal cord, leads to intense stimulation. Noxious stimulation acting on peripheral nervous system results in a long-term increase in spinal excitability, which results in the central mechanisms of allodynia and hyperalgesia. There is neuronal cooperation and enhancement of activities by tachykinins (e.g., substance P and neurokinin A) and excitatory amino acids (EAAs) (e.g., glutamate), which ultimately increase synaptic activation of dorsal horn neurons via EAA receptors. Following synthesis at the dorsal root ganglia, most of the neuropeptides are exported peripherally and not centrally, to facilitate neurogenic inflammation. Capsaicin pretreatment in neonatal rats has been found to abolish the development of thermal hyperalgesia produced in a model of neuropathic pain in rats [35, 36].

An initial local application of capsaicin is analgesic. However, its repeated application leads to desensitization, and its high concentration eventually blocks conduction of the C-fibers. This results in long-lasting sensory deficits. These properties give a logical basis for the use of capsaicin in treating pains that arise from cluster headache, complex regional pain syndrome, postmastectomy pain, postherpetic neuralgia, and diabetic neuropathy [16, 37, 38].

In his review, Caterina et al. [39] had shown that capsaicin has an expression-cloning strategy based on calcium influx to isolate a functional cDNA encoding of a capsaicin receptor from sensory neurons. Capsaicin receptor is a nonselective cation channel that is structurally related to members of the transient-receptor-potential V1 (TRPV1) family of ion channels [36, 40, 41]. The cloned-capsaicin receptor is also activated by increases in temperature in the noxious range, which suggests that it acts as a transducer of painful thermal stimuli *in vivo*.

In all, 28 mammalian transient receptor potential (TRP) cation channels have been identified and regrouped into six subfamilies [42]. These include TRPC (“canonical”), TRPV (“vanilloid”), TRPM (“melastatin”), TRPP (“polycystin”), TRPML (“mucolipin”), and TRPA (“ankyrin”). The TRPV subfamily (vanilloid receptors) comprises channels critically involved in

nociception and thermo sensing. Moreover, the TRPV 1 receptors have been found in the brain, spinal cord, peripheral neurons, smooth and cardiac muscles, vascular tissues, bronchial muscles, GIT mucosa, and the urinary bladder.

The mechanism of action of capsaicin is based on neuronal desensitization to noxious stimuli. Two forms of desensitization are apparent. One is a capsaicin-induced loss of responsiveness. This is functional and it is reversible. On the other hand is a calcium-dependent desensitization involving the activation of phosphatase and leading to the inactivation of capsaicin channel.

High doses of capsaicin may lead to neurotoxicity. Axonal and terminal degeneration and impaired nociception appear to be irreversible. Both osmotic lysis and action of calcium-dependent proteases may be responsible for capsaicin-induced neurotoxicity [43–47].

In acute pain, studies in animals have shown that systemic capsaicin relieves pain in increasing doses from 0.5 to 10 mg/kg, but nerve degeneration was noted in doses of 50 mg/kg and greater. The relief was for mechano-thermal pain [48–51]. In human studies, it requires days to weeks before beneficial effects of capsaicin can be seen [52].

With an increase in the levels of substance P in inflammatory and neurogenic joint diseases (arthritis), topical or intra-articular injections of capsaicin have shown significant improvements, as well as reductions in the level of inflammatory mediators [53–57]. In the same vein, Perkins and Campbell [58] used 6 mg/kg of intra-articular capsaicin to reverse mechanical hyperalgesia for several hours [59, 60].

In rheumatoid arthritis, the effect of capsaicin is mixed. Whereas Deal et al. [48] showed significant reduction in the level of pain intensity in 31 patients with rheumatoid arthritis of the knee following treatment with zotrix (as 0.025%) for 4 weeks, McCarthy and McCarty [62] did not observe any improvement in 7 patients with rheumatoid hands, using 0.75% capsaicin. However, Weisman et al. [49, 61, 62] reported that application of capsaicin (0.75%) for 6 weeks produced a reduction in inflammatory mediators, including substance P, in the synovial fluid of patients with rheumatoid arthritis. In osteoarthritis, there is evidence to show increase in the level of substance P in patients, [4, 53]. Randomized, controlled trials have also shown significant improvement in pain relief following treatment with capsaicin cream [23, 34, 43, 53].

With neuropathic pain in mind, animal studies using intrathecal as well as subcutaneous or topical capsaicin have produced significant improvements in the relief of hyperalgesia and pain [37, 63–66, 72]. These studies show that capsaicin-sensitive nerves have a role in thermal hyperalgesia in the animals under study [66, 67].

Studies in humans with neuropathic pain include patients with postherpetic neuralgia [51, 68], diabetic neuropathy [69], and postmastectomy pain [44]. Others include the use of capsaicin in stump or phantom pain [70], complex regional pain syndrome type I [71], trigeminal neuralgia [72], and oral neuropathic pain [64]. Capsaicin was also studied in cluster headache, and fibromyalgia [17], as well as in acute or chronic conditions, such as osteoarthritis [48, 64]; and rheumatoid arthritis [37].

Notable among these studies are those by the Capsaicin Study Group [73] with a total of 277 patients (138 capsaicin 0.075%, 139 placebo) having diabetic neuropathy. The Group reported

significant improvements in all measures (pain, walking, working, and sleeping) after administering capsaicin four times daily for up to 8 weeks. In their study, Jensen and Larson [74] found that capsaicin cream provides an alternative treatment option with a favorable outcome in painful diabetic neuropathy. Most of these studies were performed over similar periods of time, except the study by Watson et al. [75], which followed up 83 patients with postherpetic neuralgia for 2 years. The investigators found that in 86% of their patients, improvements in the pain scores were either maintained or further enhanced with no serious side effects. Furthermore, the efficacy of nasal application of capsaicin in the treatment of cluster headache had been confirmed following 7 days application of capsaicin with significant improvement when compared with placebo. The relief might have been produced through the effects of capsaicin on substance P-containing trigeminal nerve [76, 77].

Capsaicin has also been shown to relieve pruritus in patients with psoriasis [28, 70, 78], brachioradial pruritus [79], aquagenic pruritus [80], notalgia parasthetica [24], nodular prurigo [79], and pruritus produced in patients on hemodialysis [81]. In human volunteers, capsaicin treatment was found to have inhibited itch after histamine and allergen challenge. Itch is mediated by a subset of capsaicin-sensitive nociceptive neurons through the inhibition of C fiber conduction [82, 83].

The wide systemic side effects have made topical capsaicin to be more acceptable in clinical state. The main side effects are neuronal, cardiovascular, mucocutaneous tissue, or open wounds. Electron microscopic observations have revealed degeneration and glial engulfment of buttons and unmyelinated axons in the dorsal horn, 2–6 hours after neonatal subcutaneous capsaicin injections in rats. There is increased latency of the nerves; convulsion and even death may follow with very high doses of capsaicin [84, 85]. Cannabinoids have been used to attenuate capsaicin-evoked hyperalgesia [78] and low-dose lidocaine was found to reduce capsaicin-evoked secondary analgesia by a central mechanism [34].

When capsaicin is in contact with mucocutaneous tissues, such as the conjunctiva, it produces intense inflammatory reaction [86]. This is consequent upon the initial release of substance P. Cardiovascular studies on blood vessels have shown that both capsaicinoids and capsaicin could inhibit vasoconstriction induced by norepinephrine [17], and the vasodilatation effect of capsaicinoids might be due to the action of capsaicin. The compounds also cause significant decreases in platelet aggregation induced by ADP and collagen and increase blood flow in volunteers. During their study in Thailand, Jaiarj et al. [67] first noticed that people who consume large amounts of red chili peppers experienced a lower incidence of thromboembolism, or potentially dangerous blood clots.

The alternative to the mixed actions of capsaicin is being looked into through the development of purer and more potent capsaicin analogs. Refs. [72, 79, 80, 62] reported significant thermal and mechanical analgesia and antiinflammatory activity following administration of olvanil oleamide, an analog, which lacked the acute toxicity of capsaicin. Nuvanil was found to be more soluble, thus allowing for oral administration, and also showed improved oral activity and significant analgesia [6,87]. The compounds were also found to show less pungency and reduced vagal-mediated blood pressure reflexes [6,79, 80, 83, 87]. In this regard, Lee et al. [88] and Lee and Gauci [27] discussed how acute toxicity of capsaicin can be prevented through

structural modification. Moreover, Chen et al. [89] and Hua et al. [90] also reported that orally active capsaicin analog, civamide, showed a significant increase in response latency on the thermal withdrawal test that persisted for 3 days in adult rats.

5. Conclusion

From the synopsis above, it is obvious that capsaicin is a peripheral analgesic, which is cell specific. The opening of capsaicin-operated channels is required for efficacy and agonism. Improvement in the therapeutic window is required before the use of an orally active therapeutic drug. However, topical applications of capsaicin have been shown to be effective without side effect [34, 37]. There is also a growing body of evidence for the role of capsaicin in inflammation, coagulation, and gastro-intestinal function.

Author details

Adebayo Taiwo Ezekiel Jolayemi

Address all correspondence to: adebayoj@hotmail.com

Department of Anaesthesia & ICU, Goulburn Base Hospital, Australia National University, Golburn City, Australia

References

- [1] Bosland P.W. 22 Chilles: history, cultivation, and uses. Amsterdam: Elsevier Science B.V., 1994; 15: 764.
- [2] Bosland P.W. Innovative uses of an ancient crop. In: Jannick, J. (ed.). Progress in new crops. ASHS Press, Arlington, 1996; 479–487.
- [3] Hayes, A.G., Scadding, J.W., Skingle, M., and Tyers, M.B. Effects of neonatal administration of capsaicin on nociceptive thresholds in the mouse and rat. *Journal of Pharmacy and Pharmacology* 1981; 33: 183–185.
- [4] Winter, J., Woolf, C., and Lynn, B. Degenerative and regenerative responses of sensory neurons to capsaicin-induced damage. In: Wood, J.N. (ed). *Capsaicin in the Study of Pain*. London: Academic Press 1993; 139–160.
- [5] Sorkin, L.S. Basic pharmacology and physiology in acute pain process. *Anaesthesiology Clinics of North America* 1997; 15(2): 235–245.

- [6] Walpole, C.S.J., Wrigglesworth, R., Bevan, S., Cambell, E.A., Dray, A., James, I.F., Perkins, M.N., Reid, D.J., and Winter J. Analogues of capsaicin with agonist activity as novel analgesic agents; structure-activity studies. 1. The amide bond "B-region". *Journal of Medicinal Chemistry* 1993; 36: 2373–2380.
- [7] Miao, F.J., and Levine, J.D. Neural and endocrine mechanisms mediating noxious stimulus-induced inhibition of bradykinin plasma extravasations in the rat. *Journal of Pharmacology and Experimental Therapeutics* 1999; 291(3): 1028–1037.
- [8] Mogil, J.S., Yu, L., and Basbaum, A.I. Pain genes? Natural variation and transgenic mutants. *Annual Review of Neuroscience* 2000; 23: 777–811.
- [9] Sofowora, A. Proteins. In: Sofowora, A. (ed). *Medicinal plants and traditional medicine in Africa*, 2nd edition, Spectrum Books, Ibadan, Nigeria 1993; 218–220.
- [10] Lou, Y.P., Franco-Cereceda, A., and Lundberg, J.M. Different ion channel mechanisms between low concentrations of capsaicin and nicotine regarding peptide release from pulmonary afferents. *Acta Physiologica Scandinavica* 1992; 146: 119–127.
- [11] Olah, Z., Karai, L., and Iadarola, M.J. Anandemide activates vanilloid receptor 1 (VR1) at acidic p^H in dorsal root ganglia neurons and cells ectopically expressing VR1. *Journal of Biological Chemistry* 2001; 276(33): 31163–31170.
- [12] Yang, Y.L., Yao, K.H., Gu, Y.Z., Guan, B.C., and Li, Z.W. Three kinds of current in response to Substance P in bullfrog DRG neurons. *Brain Research* 2003; 981(1-2): 70–77.
- [13] Walpole, C.S.J., Wrigglesworth, R., Bevan, S., Cambell, E.A., Dray, A., James, I.F., Perkins, M.N., Reid, D.J., and Winter J. Analogues of capsaicin with agonist activity as novel analgesic agents; structure-activity studies. 1. The hydrophobic side chain "C-region". *Journal of Medicinal Chemistry* 1993; 36: 2381–2389.
- [14] Chiang, C.Y., Hu, J.W., and Sessle, B.J. NMDA receptor involvement in neuroplastic changes induced by neonatal treatment in trigeminal nociceptive neurons. *Journal of Neurophysiology* 1997; 78(5): 2799–2803.
- [15] Gronroos, M., Reunala, T., Kartamaa, M., and Pertovaara, A. Altered skin sensitivity in chronic itch: Role of peripheral and central mechanisms. *Neurosciences Letters* 1997; 228 (3): 199–202.
- [16] Simone, D.A., Baumann, T.K., and Lamotte, R.H. Late effects of prolonged topical capsaicin on cutaneous sensibility and neurogenic vasodilation in humans. *Pain* 1989; 38: 99–107.
- [17] Kim, K.J., Jeon, B.H., Kim, W.S., Park, K.R., and Choi S. Effect of capsaicin on causalgi-form pain in the rat. *Korean Journal of Physiology* 1992; 26: 143–150.
- [18] Szallasi, A., and Blumberg, P.M. Specific binding of resiniferatoxin: An ultrapotent capsaicin analog to dorsal root ganglion membranes. *Brain Research* 1990; 524: 106–111.
- [19] 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., Hughes, S.A., Rance, K., Grau, E., Harper,

- A.J., Pugh, P.L., Rogers, D.C., Bingham, S., Randall, A., and Sheardown, S.A. Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. *Nature* 2000; 40 (6783): 183–187.
- [20] Liu, L., Oortgiesen, M., Li, L., and Simon, S.A. Capsaicin inhibits activation of voltage-gated sodium currents in capsaicin-sensitive trigeminal ganglion neurons. *Journal of Neurophysiology* 2001; 85(2): 745–758.
- [21] Colpaert, F.C., Donnerer, J., and Lembeck, F. Effects of capsaicin in inflammation and on the Substance P content of nervous tissue in rats with adjuvant arthritis. *Life Sciences* 1983; 32: 1827–1834.
- [22] Vasko, M.R. Prostaglandin-induced neuropeptide release from spinal cord. *Progress in Brain Research* 1995; 104: 367–380.
- [23] Roza, C., and Reeh, P.W. Substance P, calcitonin gene-related peptide and PGE2 co-released from the mouse colon: A new model to study nociceptive and inflammatory responses in viscera, in vitro. *Pain* 2001; 93(3): 213–219.
- [24] Santicioli, P., Del Bianco, E., Geppetti, P., and Maggi, C.A. Release of calcitonin gene-related peptide-like (CRGP-LI) immunoreactivity from rat isolated isoleus muscle by low p^H , capsaicin and potassium. *Neuroscience Letters* 1992; 143: 19–22.
- [25] Leibosohn, E. Treatment of nostalgia paresthetica with capsaicin. *CUTIS* 1992; 49: 335–336.
- [26] Hajos, M., Svensson, K., Nissbrandt, H., Obal, F. Jr, and Carlsson, A. Effects of capsaicin on central monoaminergic mechanisms in the rat. *Journal of Neural Transmission* 1986; 66 (3-4): 221–242.
- [27] Lee, J.J., and Gauci, C.A. Posttherapeutic neuralgia: Current concepts and management. *British Journal of Hospital Medicine* 1994; 52 (11): 565–570.
- [28] <http://www.alternative-medicines.com/herbdesc/1capsicu.htm>, Capsicum. In: Capsicum-Red Hot Chili Peppers 2002.
- [29] Nakamura, A., and Shiomi, H. Recent advances in neuropharmacology of cutaneous nociceptors. *Japan Journal of Pharmacology* 1999; 79(4): 427–431.
- [30] Robertson, B., Docherty, R.J., and Bevan S. Capsaicin inhibits voltage-activated calcium currents in a sub-population of adult rat dorsal root ganglion neurons. *Society for Neurosciences Abstracts* 1989; 15: 354.
- [31] Sicuteri, F., Fusco, B.M., Marabini, S., Caimagnolo, V., Maggi, C.A., Geppetti, P., and Fanciullaci, M. Beneficial effect of capsaicin application to the nasal mucosa in cluster headache. *Clinical Journal of Pain* 1989; 5: 49–53.
- [32] Wallace, M.S. Advances in pain research. *Anaesthesiology Clinics of North America* 1997; 15(2): 229–234.

- [33] Dini, D., Bertelli, G., Gozza, A., and Forno, G.G. Treatment of post-mastectomy pain syndrome with topical capsaicin. *Pain* 1993; 4: 223–226.
- [34] Kinnmann, E., Nygårds, E.B., and Hansson, P. Peripheral alpha-adrenoreceptors are involved in the development of capsaicin induced on-going and stimulus evoked pain in humans. *Pain* 1997; 69 (1-2): 79–85.
- [35] Simone, D.A., and Ochoa, J. Early and late effects of prolonged topical capsaicin on cutaneous sensibility and neurogenic vasodilatation in humans. *Pain* 1991; 47: 285–294.
- [36] Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., and Julius, D. The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature* 1997; 389 (6653): 783–784.
- [37] Caterina, M.J., and Julius, D. The vanilloid receptor: A molecular gateway to the pain pathway. *Annual Review of Neuroscience* 2001; 24: 487–517.
- [38] Cesare, P., Moriondo, A., Vellani, V., and McNaughton, P.A. Ion channels gated by heat. *Proceedure of National Academy of Sciences of United States of America*. 1999; 96 (14): 7658–7663.
- [39] Chaudhary, P., Martenson, M.E., and Baumann, T.K. Vanilloid receptor expression and Capsaicin excitation of rat dental primary afferent neurons. *Journal of Dental Research* 2001; 80 (6): 1518–1523.
- [40] McMahon, S.B., Lewin, G., and Bloom, S.R. The consequences of long-term topical capsaicin application in the rat. *Pain* 1991; 44: 301–310.
- [41] Cervero, F., and McRitchie, H.A. Effect of neonatal administration of capsaicin in several nociceptive systems of the rat. In: Bonica, J.J., Liebeskind, J.C., and Albe-Fessard, D.G. (eds), *Advances in Pain Research and Therapy*. New York: Raven Press; 1997; 4: 87–94.
- [42] Peikert, A., Henrich, M., and Ochs, G. Topical 0.025% capsaicin in chronic post-herpetic neuralgia: Efficacy, predictors of response and long-term course. *Journal of Neurology* 1991; 238: 452–456.
- [43] Rang, H.P., and Urban, L. New molecules in analgesia. *British Journal of Anaesthesia* 1995; 75: 145–156.
- [44] Gamse, R. Capsaicin and nociception in the rat and mouse. Possible role of Substance P. *Naunyn-Schmiedeberg's Archive of Pharmacology* 1982; 320: 205–216.
- [45] Vriens, J., Appendino, G., and Owsiank, G. Pharmacology of vanilloid transient receptor potential cation channels. *Molecular Pharmacology* 2009; 75 (6): 1262–1279.
- [46] Carpenter, S.E., and Lynn, B. Vascular and sensory responses of human skin to mild injury after topical treatment with capsaicin. *British Journal of Pharmacology* 1981; 73: 755–758.

- [47] Dray, A., Bettany, J., and Forster P. Actions of capsaicin on peripheral nociceptors of the neonatal rat spinal cord-tail in vitro: Dependence of extracellular ions and independence of second messengers. *British Journal of Pharmacology* 1990; 101: 727–733.
- [48] Deal, C.L., Schnitzer, T.J., Lipstein, E., Seibold, J.R., Stevens, R.M., Levy, M.D., Albert, D., and Renold, F. Treatment of arthritis with topical capsaicin: A double-blind trial. *Clinical Therapeutics* 1991; 13: 383–395.
- [49] McCarty, D.J., Csuka, M., McCarthy, G., and Trotter, D. Treatment of pain due to fibromyalgia with topical capsaicin: a pilot study. *Seminars in Arthritis and Rheumatism* 1994; 23 (Suppl 3): 41–47.
- [50] Weisman, M.H., Hagaman, C., Yaksh, T.L., and Lotz, M. Preliminary findings in the role of neuropeptides suppression by topical agents in the management of rheumatoid arthritis. *Seminars in Arthritis and Rheumatism* 1994; 23 (suppl 3): 18–24.
- [51] McCleskey, E.W., and Gold, M.S. Ion channels of nociception. *Annual Review of Physiology* 1996; 61: 835–856.
- [52] Wood, J.N., Coote, P.R., Minhas, A., Mullaney, I., McNeill, M., and Burgess, G.M. Capsaicin-induced ion fluxes increase cyclic GMP but not cyclic AMP levels in rat sensory neurons in culture. *Journal of Neurochemistry* 1989; 53: 1203–1211.
- [53] Watson, C.P.N., Evans, R.J., and Watt, V.R. The post-mastectomy pain syndrome and the effect of topical capsaicin. *Pain* 1989; 38: 177–186.
- [54] Baron, R., Wasner, G., and Lindner, V. Optimal treatment for phantom limb pain in the elderly. *Drugs and Aging* 1998; 12(5): 361–376.
- [55] Berring, P., Arendt-Nielsen, I., and Soderberg, U. Argon laser induced cutaneous sensory and pain thresholds in post-herpetic neuralgia. Quantitative modulation by topical capsaicin. *Acta Dermatology Venerology* 1990; 70: 121–125.
- [56] Woolf, C.J., Bennett, G.J., Doherty, M., Dubner, R., Kidd, B., Koltzenburg, M., Lipton, R., Loeser, J.D., Payne, R., and Torcbjork, E. Towards a mechanism-based classification of pain? *Pain* 1989; 77: 227–229.
- [57] Kroll, F., Karlsson, J.A., Lundberg, J.M., and Persson, C.G. Capsaicin-induced bronchoconstriction and neuropeptide release in guinea-pig perfused lungs. *Journal of Applied Physiology* 1990; 68: 1679–1687.
- [58] Perkins MN and Campbell EA. Capsezepine reversal of the antinociceptive action of capsaicin in vivo. *British Journal of Pharmacology*. 1992; 107 (2): 329–333.
- [59] Petersen, K.L., and Rowbotham, M.C. A new human experimental pain model: The heat/capsaicin sensitization model. *Neuroreport* 1999; 10(7): 1511–1516.
- [60] Leis, S., Weber, M., Isselmann, A., Schmelz, M., and Birklein, F. Substance P-induced protein extravasation is bilaterally increased in complex regional pain syndrome. *Experimental Neurology* 2003; 183 (1): 197–204.

- [61] Campbell, E.A., Bevan, S., and Dray, A. Clinical applications of capsaicin and its analogues. In: Wood, J.N. (ed). *Capsaicin in the Study of Pain*. London Academic Press 1993; 255–272.
- [62] McCarthy, G.M. and McCarthy, D.J. Effect of topical capsaicin in the painful osteoarthritis of the hands. *Journal of Rheumatology* 1992; 19: 604–607.
- [63] Watt, J.M., and Breyer-Brandwijk, M.G. *The medicinal and poisonous plants of Southern and East Africa*. 1962; 862–942.
- [64] Sinoff, S.E., and Hart, M.B. Topical capsaicin and burning pain. *Clinical Journal of Pain* 1993; 9: 70–73.
- [65] Capsaicin Study Group. Treatment of painful diabetic neuropathy with topical capsaicin. A multi-centre, double blind, vehicle-controlled study. *Archives of Internal Medicine* 1999; 151: 2225–2229.
- [66] Koppert, W., Ostermeier, N., Sittl, R., Weidner, C., and Schmelz, M. Low-dose lidocaine reduces secondary hyperalgesia by a central mode of action. *Pain* 2000; 85(1): 217–224.
- [67] Jaiarj, P., Saichompoo, S., Wongkrajang, Y., Vongswan, N., Peungvicha, P., and Jiratchariyakul, W. Cardiovascular actions of capsaicinoids extract from Thai capsicum. *Thai Journal of Phytopharmacy* 1998; 5(2): 1–13.
- [68] Docherty, R.J., Robertson, B., and Bevan, S. Capsaicin causes prolonged inhibition of voltage-activated calcium currents in adult rat dorsal root ganglion neurons in culture. *Neuroscience* 1991; 40: 513–521.
- [69] Goodless, D.R., and Eaglstein, W.H. Brachioradial pruritus: Treatment with topical capsaicin. *Journal of the American Academy of Dermatology* 1993; 29: 783–784.
- [70] Abdala, A.P., Haibara, A.S., and Colombari, E. Cardiovascular responses to Substance P in the nucleus tractus solitarii: Microinjection study in conscious rats. *American Journal of Physiology of Heart and Circulation Physiology* 2003; 285(2): 891–898.
- [71] Levin, J.D., Clarke, R., Devor, M., Helms, M.A., Moskpwitz, M.A., and Basbaum, A.I. Intraneuronal Substance P contributes to the severity of experimental arthritis. *Science* 1984; 226: 547–549.
- [72] Brand, L.L., Berman, E., Schwen, R., Loomans, M., Janusz, J., Bonne, R., Maddin, C., Gardner, J., LaHamn, T., Farmer, R., Jones, L., Chiaabrande, C., and Fanelli, R. NE-19950: A novel, orally active anti-inflammatory analgesic. *Drugs in Experimental and Clinical Research* 1987; 13: 259–265.
- [73] Faulkner, D.C., and Growcott, J.W. Effects of neonatal capsaicin administration on the nociceptive response of the rat to mechanical and chemical stimuli. *Journal of Pharmacy and Pharmacology* 1980; 32: 657–658.

- [74] Shir, Y., and Seltzer, Z. A-fibers mediate thermal mechanical hyperesthesia and allodynia and C-fibers mediate thermal hyperalgesia in a new model of causalgiform pain disorders in rats. *Neuroscience Letters* 1990; 115: 62–67.
- [75] Maggi, C.A., Patacchini, R., Santiciolli, P., Giuliani, S., Delbianco, F., Geppetti, P., and Meli, A. Protective action of ruthenium red toward capsaicin desensitization of sensory fibers. *Neuroscience Letters* 1988; 88: 201–205.
- [76] Menkes, C.J., Renoux, M., Loussadi, S., Mauborgne, A., Bruxelle, J., and Cesselin, F. Substance P (SP) levels in synovial tissue and synovial fluid from rheumatoid arthritis (RA) and osteoarthritis (OA) patients. *Journal of Rheumatology* 1993; 20: 714–717.
- [77] Jensen, P.G., and Larson, J.R. Management of painful diabetic neuropathy. *Drugs* 2001; 18(10): 737–749.
- [78] Kowalski, M.L., Dietrich-Milobedzi, A., Majkowska-Wojciechowska, B., and Jarzebska, M. Nasal reactivity to capsaicin in patients with seasonal allergic rhinitis during and after the pollen season. *Allergy* 1999; 54 (8): 804–810.
- [79] Brand, L.M., Skare, K.L., Loomans, M.E., Reller, H.H., Schwen, R.J., Lade, D.A., Bohne, R.L., Maddin, C.S., Moorehead, D.P., Fanelli, R., Chiabrando, C., Castelli, M.G., and Tai, H.H. Anti-inflammatory pharmacology and mechanism of the orally active capsaicin analogs, NE-19950 and NE-28345. *Agents and Clinical Research* 1990; 31: 329–340.
- [80] Breneman, D.L., Cardone, J.S., Blumack, R.F., Lather, R.M., Searle, E.A., and Pollack, V.E. Topical capsaicin treatment of hemodialysis-related pruritus. *Journal of the American Academy of Dermatology* 1992; 26: 91–94.
- [81] Yakish, T.L. Spinal systems and pain processing: Development of novel analgesic drugs with mechanistically defined models. *Trends in Pharmacological Science* 1999; 20: 329–337.
- [82] Yeats, J.C., Boddeke, H.W., and Docherty, R.J. Calcium dependent and independent desensitization in rat dorsal root ganglion neurons is due to activation of calcineurin. *British Journal of Pharmacology* 1992; 107: 238P.
- [83] Johanek, L.M., Heitmiller, D.R., Turner, M., Nader, N., Hodges, J., and Simone, D.A. Cannabinoids attenuate capsaicin-evoked hyperalgesia through spinal and peripheral mechanisms. *Pain* 2001; 93(3): 303–315.
- [84] Knight, T.E., and Hayashi, T. Solar (brachioradial pruritus)-response to capsaicin cream. *International Journal of Dermatology* 1994; 33: 206–209.
- [85] Jancso, G.K., and Jancso-Gabor, A. Pharmacologically induced selective degeneration of chemo-sensitive primary sensory neurons. *Nature* 1977; 270: 741–743.
- [86] The phytochemical collection, 2002 In molecular expressions: The phytochemical collection. <http://micro.magnet.fsu.edu/phytochemicals/index.html>

- [87] Watson, C.P.N. Evans, R.J. and Watt, V.R. The post-mastectomy pain syndrome and the effect of topical capsaicin. 1989 *Pain*; 38: 177-186.
- [88] Lee, S.S., Sohn, Y.W., Yoo, E.S., and Kim, K.H. Neurotoxicity and long lasting analgesia induced by capsacinoids. *Journal of Toxicology Science* 1991; 1: 3–20.
- [89] Chen, I.J., Yang, J.M., Yeh, J.L., Wu, B.N., Lo, Y.C., and Chen, S.J. Hypotensive and antinociceptive effects of ether-linked and relatively non-pungent analogues of N-nonanoyl nanillylamide. *European Journal of Medicinal Chemistry* 1992; 27: 187–192.
- [90] Hua, X.Y., Chen, P., Hwang, J., and Yaksh, T.L. Antinociception induced by civamide: An orally active capsaicin analogue. *Pain* 1997; 71(3): 313–322.