

THERAPEUTIC EFFECTS OF CAPSAICIN ON PAIN MANAGEMENT

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ABSTRACT

Pain is an undesirable sensory experience that occurs from the noisome stimulus, it becomes a warning sign of an upcoming disease or existing disease thereby signaling immediate attention. There exists a variety of pharmacological and non-pharmacological methods to alleviate pain, with their own effects and impacts on health. The natural herb capsicum, used in most families as a spice is also found to have the therapeutic effects of for treating cardiovascular disorders, respiratory issues, gastrointestinal problems, urological disorders, cancer, diabetic peripheral neuropathy, obesity and pain reduction, especially in osteoarthritis and rheumatoid arthritis. It acts as a counter-irritant for various conditions like rheumatism, lumbago and neuralgia. It reduces pain by aiding in the depletion of substance-P and increases the activation of intracellular calcium by activating the calcium channel. The stimulation of transient receptor potential vanilloid 1 (TRPV1) causes effects like analgesia, anti-infectious, anti-carcinogenic and antioxidant. It is permissible to use capsaicin in low concentrations such as in creams, lotions, gel patches and nasal sprays. High-concentration capsaicin is available in the form of oral formulations, intradermal, subcutaneous and intravenous. Capsaicin is mostly available in topical form, in many concentrations such as 0.025%, 0.0355%, 0.075% and 0.10%. It has been permitted to use capsaicin to the maximum concentration of 8%. Capsaicin is safe to use even in pregnancy, lactation, children and adolescents but is contraindicated for children less than 2 years old as well as for people with bleeding disorders.

Keywords: Capsicum, Capsaicin, Pain, Substance-P, Commercial forms, Relief

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INTRODUCTION

Pain is a major concern for all individuals. Pain is an undesirable sensory and emotional experience. It is a complicated experience that occurs for the noisome stimulus. Pain occurs for various causes either to alert the upcoming potential damage to the body part or as an indication that the body needs a period of rest. The two types of pain are acute and chronic. Acute pain cautions the ensuing danger, whereas chronic pain is usually associated with existing diseases in the body (Świeboda *et al.* 2013) The pain stimulus is initially detected by a membrane-bound nociception and transduces to the brain through a structural protein, ion channels and neurotransmitters. However, pain is a warning sign of an upcoming disease or a sign of an existing disease that requires urgent attention. Pain can be treated either with medications or non-drug therapies or in combination (Cheng, Rutherford and Singh 2019). The medical management of pain includes various chemical combinations that act on the brain and a few on the muscles and the topical areas.

This combination of drugs includes various groups of opioid and nonopioid analgesics, tramadol, antidepressants and anticonvulsants, and for relieving pain in the muscles topical analgesics are used. Those drugs either ingested orally or applied topically or injected through muscles or intravenously will have adverse effects on long-term use (Park and Moon 2010). The other non-drug approach for pain includes physical, cognitive and behavioural therapies. The effect of acupuncture which involves stimulating the particular nerve through small needles and yoga which involves the coordinated effect of body, muscles and breathing are yet to be scientifically proved (Case *et al.* 2021). The unpleasant effects of the pain medications and the restricted efficacy of the long-term therapies made it tough to treat pain (Gauntlett-Gilbert and Brook 2018). In this challenging context, there is a need to poke up for an alternative with no side effects and a reclamation that lasts long.

The effect of capsicum to relieve pain has been tested and proved in various researches. Capsicum generally contains non-volatile alkaloid compounds which are needed for the analgesic effect. It acts as a counter-irritant for various conditions like rheumatism, lumbago and neuralgia. Intake of capsicum through the diet or its chemical form trans-8-methyl-N-vanillyl-6-nonenamide available commercially is more efficient in treating cardiovascular disorders, respiratory issues, gastrointestinal problems, urological disorders, cancer, diabetic peripheral neuropathy, obesity, pain reduction, especially in osteoarthritis, rheumatoid arthritis (Watanabe *et al.* 2020). The medical effects of capsicum like analgesia, weight loss, anti-infectious, anti-carcinogenic and anti-oxidant are due to the stimulation of transient receptor potential vanilloid 1 (TRPV1), a protein in humans encoded with TRPV1 gene thus it also acts as a capsaicin receptor. It absorbs easily up to 94% when used topically or orally helps in the reduction of pain and systemic diseases (Fattori *et al.* 2016).

Physiology of Pain

Pain is a subjective feeling that can be experienced with a series of steps which is constructively called the pain pathway. The pain pathway includes the following steps: nociception, transduction, transmission, perception and modulation (Yam *et al.* 2018). Figure 1 given below depicts the afferent pain pathway.

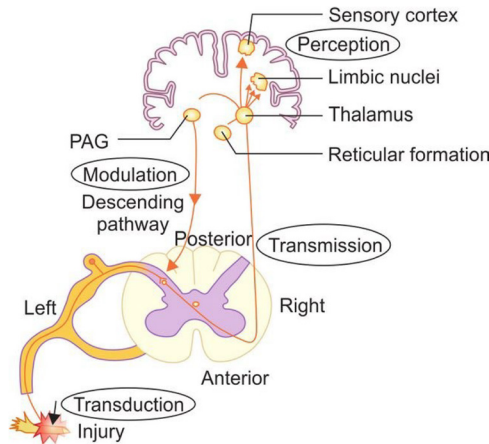


Figure 1: Basic concepts of pain.
Source: Sharma and Das (2018).

Nociception

Nociception is a process of receiving a noxious stimulus by the receptors of pain in the skin or tissue. The pain receptors are usually termed nociceptors. The noxious stimulus may occur due to the thermal, mechanical or chemical stimulus. The noxious stimulus hurts the tissue that comes in contact with the stimulus. Nociceptors at the site of injury or damage will get triggered.

Transduction

Transduction is the process by which the afferent nerve endings aid in the transmission of noxious pain stimulus into nociceptive impulse. The pain signals received by the nociceptors are conducted by the A-delta fibre which conducts the signals fast and type-C fibre which is a slow-conducting fibre. Type-C fibres are also termed silent nociceptors. These nociceptors will respond to external stimuli only with the presence of inflammatory mediators. The inflammatory mediators which stimulate type-C fibres include globulin, protein kinase, arachidonic acid, histamine, substance-P, nerve growth factor and calcitonin gene-related peptide.

Transmission

Transmission is the process by which pain impulses are traveled to the dorsal horn of the spinal cord and then along the sensory tracts to the brain. The primary sensory neurons of the peripheral nervous system play a vital role in transmitting pain signals. They are the active senders and receivers of chemical and electrical signals which are termed neurotransmitters. The axons of these nerves diverge and form a dorsal root ganglion near the spinal cord. Thus, the signals received by the primary afferent (sensory) neurons transmit to the contralateral thalamus which in turn projects to the somatosensory pathway, frontal cortex and limbic system.

Perception

It is the process being felt with the uncomfortable sensation in a specific area. Perception is the continuation of the transmission in the pain pathway and depends on the extent of pain signals transmitted through the thalamus to the cortex and the limbic system (Baliki and Apkarian 2015).

Modulation

Modulation is the process of increasing or decreasing the intensity of the pain signals which occurs usually on the dorsal horn of the spinal cord and also in the ascending and descending pathways of the pain. According to gate control theory, the substantia gelatinosa of Rolando, a grey matter available in the dorsal horn of the spinal cord, acts as a gate to send and modulate the electrical and chemical signals of pain. The type-A fibres are fast-acting and carry the non-nociceptive impulses at a fast rate to the brain. On the other hand, type-C fibres are slow-acting and carry nociceptive impulses.

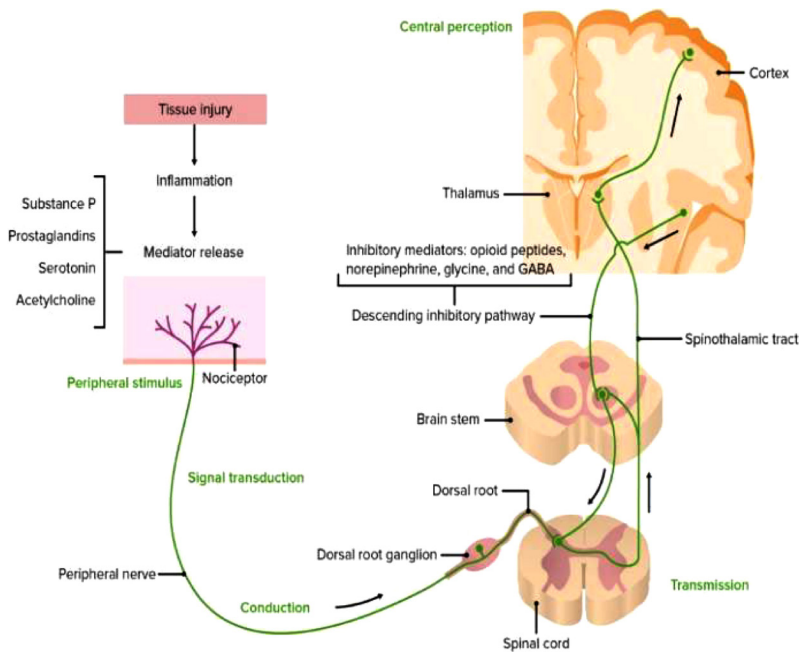


Figure 2: The physiology of pain pathway.

Source: Lecturio - <https://app.lecturio.com/#/article/3862>

The substantia gelatinosa modulates the transmission of impulses either by presynaptic inhibition or facilitation of the afferent nerves. Type-A fibre stimulates the gating component and thereby causes synaptic inhibition which in turn results in hypoalgesia where the person feels less or no pain. Once the activity of the type-C fibres reaches the substantia gelatinosa, the gate opens and causes disinhibition of the synaptic transmission leading to the transmission of pain signals to the brain and causing the perception of pain which is termed a state of hyperalgesia. The merge of the inputs from the sensory

neurons, spinal cord and the brain is usually determined by the neurotransmitters called opioids, glycine, norepinephrine and gamma-amino butyric acid (Mendell 2014). The process of gate control theory is explained in Figure 2.

Capsaicin

Chilli, with the botanical name *Capsicum annum* Linn, is a natural herb and the most available ingredient used for cooking, which has medicinal properties, too. Hence it is also used in alternative or traditional medicine for treating patients. The chemical form of capsaicin is expressed as trans-8-methyl-N-vanillyl-6-nonenamide. Capsaicin, a secondary metabolite is the most commonly available natural compound in chilli. Chemical compounds like alkaloids, terpenoids, steroids and saponins associated with secondary metabolites enhance the medical effects of capsaicin. The capsaicinoid compounds are made of vanillamine and fatty acids chained together called amide compounds. The pungent or the hot taste and the odour of the capsicum are facilitated by the capsaicinoid compounds which include nordihydrocapsaicin, capsaicin, dihydrocapsaicin, norcapsaicin, homodihydrocapsaicin, homocapsaicin and nonivamide, 69% of the capsaicinoids compound is piled with capsaicin.

Capsaicin also contains the components of vitamins A and C such as carotene, capsanthin, capsorubin and zeaxanthin. It also possesses the microminerals like iron, potassium, calcium, phosphorous and niacin. Capsaicin is found in higher quantities in the dry chilli than the fresh ones, and hence mature dried red chili is hotter than the green chili (Popelka *et al.* 2017). The elements available in the capsicum are efficient as a stimulant of gastric acid secretion and also prevent infection in the digestive system. The elements like capsiol have analgaesic properties and are also used to reduce asthma and itching. Capsaicin is extracted artificially using ethanol or acetone and can be prepared in the form of an oleoresin. This form of capsaicin has a carminative effect. It acts as a neuro stimulant and counter-irritant for lumbago, neuralgia and rheumatoid. It is also used in the treatment of impotence, anti-helminthic, anti-flatulent, antifungal, expectorant and analgesic (Kamal, Chowdhury and Chowdhury 2015).

Properties of capsaicin and its therapeutic benefits

Capsaicin is an organic compound, contains a group of compounds called alkaloids. The chemical form of capsaicin is expressed as trans-8-methyl-N-vanillyl-6-nonenamide (Clark and Lee 2016) and has an impact on thermoregulation and adipose tissue metabolism (Adaszek *et al.* 2019). The stability of capsaicin is based on sensorial traits and sensitivity to environmental, and food processing conditions. Hence the capsaicin can be encapsulated with nano fibres of zein mate which increases the thermal stability by 50%. The encapsulated fibres also have an antimicrobial effect against *Staphylococcus aureus* and *Escherichia coli* (Rezazadeh *et al.* 2022). Capsaicin stimulates the tumour suppressive signaling pathway and inhibits the oncogenic signaling pathway and tumour promoters (Clark and Lee 2016).

Capsaicin decreases the secretion of acid in the gastric mucosa and helps in the prevention or healing of gastric ulcers (Srinivasan 2016). Substance-P in the type-A fibres which possess the TRP action channel also known as VR1 is responsible for the transmission of the pain signals in the afferent nerves. Capsaicin acts as an analgaesic by depleting the substance-P. Capsaicin also has an effect on pain, particularly during the inflammatory process by stimulating VR1 (vanilloid receptor type-1 agonists), which has an important role in the hyperalgaesia state of the inflammatory process. The antinociception created by capsaicin has also had an effect on the appearance of the wound.

The stimulation of the sympathoadrenal system enhances the metabolism and decreases the body fat mass and can be utilised in the treatment of obesity. Capsaicin also aids in decreasing pruritis by depleting the substance-P which is also responsible for the transmission of pruritis in dialysis patients. Capsaicin creates a heat sensation in the body by stimulating TRPV1 (a transient receptor potential cation channel subfamily vanilloid member) (Novakova-Tousova *et al.* 2007). Regular intake of capsaicin-containing chillies or the supplementation of capsaicin has an effect on postprandial hyperglycaemia and hyperinsulinaemia among women with gestational diabetes mellitus. Capsaicin aids in the reduction of islet infiltration and beta cell stress in neonates, and also helps in insulin resistance by suppressing the TRPV1-expressing pancreatic sensory neurons (Yuan *et al.* 2016). Capsaicin by stimulating TRPV1, activates the calcitonin gene-related peptide (CGRP) thereby, helping in the control of blood pressure. Activation of TRPV1 decreases the storage of lipids and atherosclerotic effect in the aortic sinuses thereby slowing the process of atherosclerosis (Kang *et al.* 2010).

Mechanism of capsaicin on pain relief

The initial works of the action of capsicum have been tested by animal research in monkeys and rats (Sluka and Willis 1997). The dorsal root ganglion (DRG) of the spinal cord contains the influx of ions and calcium determination excited by the capsicum. In later years, the research on the TRPV1 which produces a pain-like experience by activating the vanilloid system has given wisdom and changed the way of understanding pain in different concepts (Wang *et al.* 2016). Similarly, the action of capsaicin on the activation of C polymodal nociceptors in the type-C fibres in cats and the reduction of thermal threshold has also been evidenced in animal research. Mitogen-activated protein kinase (MAPK) also has evidence of causing the effect of pain and capsaicin in the periphery and dorsal horn of the spinal cord increases the phosphorylation of p38 MAPK thereby decreasing the effect of pain (Sweitzer *et al.* 2004).

TRPV1 a vanilloid system stimulates the activation of CGRP and by administering the capsaicin antagonist intrathecally inhibits or reduces the development and maintenance of pain and secondary allodynia. Reactive oxygen species (ROS) have a role in central sensitisation leading to pain effects. The post-translational modification can be a result of ROS as it acts on its proteins such as cysteine and serine. Treatment with ROS reduces the activation of neurons in the dorsal horn of the spinal cord. Capsaicin reduces this neural responsiveness and thereby decreases the primary and secondary hyperalgesia state of pain keratinocytes which lie proximally to the nociceptors also have a role in causing pain.

Capsaicin stimulates the TRPV1-expressing keratinocytes and thus produces the paw licking behaviour during pain (Pang *et al.* 2015). Substance-P and CGRP are the two neuropeptides that have an effect in the signaling of pain along with the TRPV1 mediate the visceral pain, contribute to the emotional effect of visceral pain and also cause the process of inflammation in the case of arthritis (Lapointe *et al.* 2015). Capsaicin co-administered with QX-314, a membrane-impermeable sodium channel blocker blocks the sodium inward currents in the DRG of the spinal cord and thus produces the effect of analgesia (Binshtok, Bean and Woolf 2007). Capsaicin changes the pore size of the TRPV1 which leads to discrimination between monovalent and divalent cations which makes sustainability.

The differentiation between the cations is possible by the phosphorylation of TRPV1 serine 800 residues by PKC (protein kinase which aids in signaling pathways). This phosphorylation will increase the permeability to large cations and aids in the proportioning sensitisation of TRPV1, thereby, enhancing the inward currents of sodium. N- arachidonoyl dopamine (NADA), piperine and resiniferatoxin (RTX) are the TRPV1 agonists. They help

in the discrimination and selectivity of the pattern of ions. The study found that capsaicin binds to the TRPV1 pockets as a unique molecule (Yang *et al.* 2015). TRPV1-TRPA1 (transcription associated protein) is a well-noticed receptor-receptor interaction attributed to the formation of heterodimers between them. Studies also show that a transmembrane receptor called Tmem 100 is expressed additionally with TRPV1 and TRPA1 complex in the DRG of the spinal cord (Elokely *et al.* 2016). The mechanism of activation and the series of events followed is explained in Figure 3.

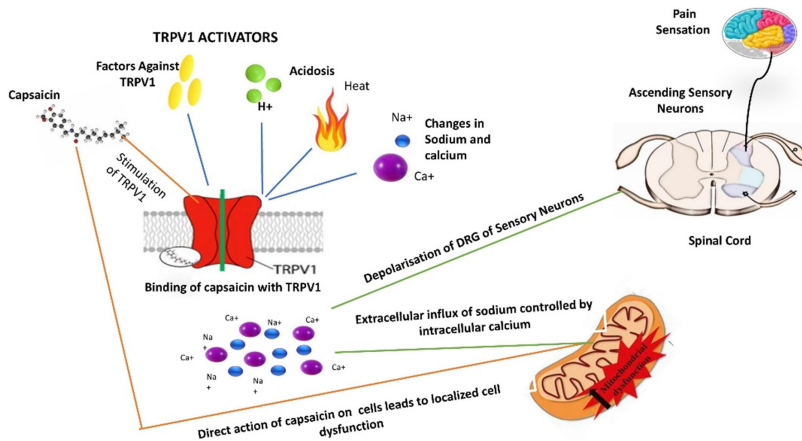


Figure 3: Mechanism of activation of TRPV1 on pain management.

Capsaicin initially produces pain and on high or repeated doses produces an effect of analgesia to thermal, mechanical and chemical noxious stimuli (Palazzo *et al.* 2002). TRPV1 by exposure to capsaicin becomes in the refractory state which is generally stated as desensitisation leading to inhibition of the receptor function. The process of desensitisation includes depletion of neuropeptides such as substance-P in the nerve fibres that expresses TRPV1 and an increase of intracellular calcium levels by altering the calcium channels (Communanza *et al.* 2011). The changes in the calcium channels include the activation of calcium-dependent proteins, binding of calmodulin (CaM) in the adenosine triphosphate (ATP) pockets (usually referred to as energy currency of the cell) of TRPV1-activator of RNA decay (ARD), phosphorylation of calcineurin, a calcium-dependent enzyme dephosphorylates Thr370 and regulation of HVA (high voltage activated) by calcineurin limits the calcium influx in DRG neurons such a mechanism induces the desensitisation of TRPV1 thereby causing capsaicin-induced analgesia (Salas, Kenneth and Armen 2009).

By activating TRPV1, capsaicin inhibits piezo proteins i.e., the family of mammalian cation that responds to mechanical stretch. It occurs due to the activation of phospholipase that depletes phosphoinositides. Injection of phosphoinositides in the cytosol causes the depletion of piezo proteins and the depletion of phosphoinositides correlates with the stimulation of piezo proteins. Thus, the application of capsaicin topically aids in the activation of phospholipase thereby inhibiting the action of piezo proteins which is responding to the mechanical stretch. Thereby capsaicin acts as a local analgesic (Borbiro, Badheka and Rohacs 2015). The most common mechanism in the understanding of capsaicin-induced analgesia is apoptosis via caspase activation. Capsaicin causes fragmentation of the DNA leading to a decrease in the nucleus of the cell in a caspase manner. This further causes cell death of the sensory neurons.

Capsaicin acts as an analgesic by depleting the sensory neurons. This process is also related to the mitochondrial permeability of the cell by activating the TRPV1 with capsaicin. The apoptosis process of the cell also occurs by the extracellular influx of sodium by TRPV1; controlled by calcium in the intracellular complex. The intracellular and extracellular changes triggered by TRPV1 lead to cell swelling and bleb formation in the membrane causing cell death (Shin *et al.* 2003). TRPV1-induced desensitisation has a longer effect in inflammatory conditions compared to basal conditions.

A short period of analgesia has been produced in the rat by the injection of capsaicin in the dorsal portion of the periaqueductal gray in rats. The activation of inhibitory descending pain mechanisms has been found by the injection of capsaicin in the ventrolateral PAG (vlPAG) site in animal studies. The inhibitory mechanism can be activated by the TRPV1 which in turn releases glutamate resulting in the activation of OFF cells and inhibition of ON cells thereby, reducing thermal hyperalgesia. The injection of capsaicin in rostral ventromedial medulla (RVM) inhibits the pain in the inflammatory phase in rats and has also been evidenced in animal studies. RVM usually plays a key role in the descending pain control pathway and contributes to the development and maintenance of pain.

Available forms of capsaicin

Capsaicin is available both in natural form and pharmaceutically prepared form. In natural form, it is available as chilli peppers. In the synthetic form, it exists in low concentration forms include creams, lotions, gel patches and nasal sprays, and in high-concentration forms. It is available in oral formulations, intradermal, subcutaneous and intravenous forms.

Topical form capsaicin for pain management

Capsaicin is available in topical forms with many brand names. It is used to relieve musculoskeletal pain as an over-the-counter medicine. Off the label, it is also used as a symptom treatment for diabetic neuropathic pain. In topical form, it is available in many concentrations such as 0.025%, 0.0355%, 0.075% and 0.10%. As a topical gel and in liquid form, it is available in a concentration of 0.025%. The administration of high doses of capsaicin such as 8% in topical form has also been approved in European countries and the USA for the treatment of diabetic neuropathy and post-herpetic pain. It can be applied for 3 times per day to treat osteo and rheumatoid arthritis, diabetic neuropathy, and migraine. In diabetic neuropathy, it is allowed to use capsaicin 4 times a day but it is strictly cautioned that the dose of applications should not exceed 4 times a day (Gutierrez *et al.* 2021).

Oral form capsaicin for pain management

Ingesting capsicum which occurs in chilli orally is found to be directly absorbed in the gastrointestinal (GI) system and observed in the plasma within 15 min and not found in the plasma after 90 min. Studies with oral administration of capsicum with 5 mg and 10 mg have been done and concluded that oral administration of capsicum resulted in GI irritation. However, GI irritation can be reduced with the encapsulation of capsicum with cyclodextrin. Despite the side effects, it has been found that oral administration of capsaicin in candy form temporarily relieves pain due to oral mucositis in cancer patients after chemotherapy (Arnold, Bruce-Low and Sammut 2016).

Intranasal form of capsaicin

Capsaicin is found to be effective in relieving rhinitis when given in the intranasal form. It inhibits the hypersensitivity of TRP channels which are responsible for the symptoms of rhinitis (Singh and Bernstein 2014). A homeopathic preparation of capsicum annuum and eucalyptol nasal sprays, a dose of 4 µg 3 times a day for three consecutive days is found effective for nonallergic and non- infectious perennial rhinitis (Gevorgyan *et al.* 2015).

The injection form of capsaicin for pain management

Injection capsaicin with 0.5 mg–1.0 mg was tested for its efficiency in relieving osteoarthritis and compared with the placebo. The study results showed that injection capsaicin was found effective in relieving pain in the knees which was concluded after a follow-up for 12 weeks. A synthetic form of capsaicin (CNTX 4975) was developed and tested for its efficiency. It was proven effective in the treatment of osteoarthritis. Injecting capsaicin intradermally causes degeneration of epidermal nerve fibres more effectively than topical administration (Campbell *et al.* 2021).

Uses of capsaicin in pain treatment Capsaicin is useful in the treatment of different types of pain such as neuropathic pain, post-surgical neuropathic pain, complex regional pain, post-herpetic neuralgia, chronic musculoskeletal pain, painful diabetic neuropathic pain and cluster headache attacks (Burness and McComack 2016).

Pain in cancer

The provision of capsaicin in the form of candy relieves pain caused due to mucositis; the mostcommon difficulty faced by the patient during the treatment of cancer.

Post-herpetic neuralgia

A topical application of an 8% capsaicin patch aids in the relief of pain due to herpes infection within 12 weeks.

Post-traumatic neuropathic pain

The use of 8% capsaicin at the site of allodynia had a betterment in the pain which lasts for about 18 months.

Side effects and contraindications

Topical administration of capsaicin produces side effects like burning sensation, redness, and itching on the site of application; side effects like cough and throat irritation have also been noticed in a few. Some serious complications like pain and swelling, in the area and eye irritation were also noticed rarely. Capsaicin cream should not be applied to open wounds. It should be used only on nonirritant, clean and dry skin. Topical administration of capsaicin is safe to use even in pregnancy, lactation, children, and adolescents which should be used not more than 4 times a day. Capsaicin is contraindicated for children less than 2 years and people with bleeding disorders since capsaicin is at risk to cause bleeding (Basith *et al.* 2016).

CONCLUSION

The therapeutic effects of capsaicin have reduced the unpleasant sign of pain by aiding in the depletion of substance-P and increases the activation of intracellular calcium by activating the calcium channel. The available forms low and high concentration of capsaicin has an effect on pain reduction, particularly during the inflammatory process by stimulating VR1 agonists, which has an important role in the hyperalgesia state of the inflammatory process. The stimulation of TRPV1 in treating the minor ailments and has the effects like anti-infectious, anti-carcinogenic, anti-oxidant, analgesic effects especially in osteoarthritis and rheumatoid arthritis. The recommended dose of capsaicin is safe to use even in antenatal and nursing mothers and children more than 2 years old. Thus, capsicum, a natural herb, turns into an available medicine to manage pain at every house in this current decade.

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