Capsaicin: Plants of the Genus *Capsicum* and Positive Effect of Oriental Spice on Skin Health

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Keywords

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Abstract

Background: Capsaicin, the main pungent ingredient in hot chili peppers, causes excitation of small sensory neurons. It also provides the basic pungent flavor in *Capsicum* fruits. **Summary:** Capsaicin plays a vital role as an agonist for the TRPV1 (transient receptor potential cation channel, subfamily V, member 1) receptor. TRPV1 is essential for the reduction of oxidative stress, pain sensations, and inflammation. Therefore, it has many pros related to health issue. Activation and positive impact of TRPV1 via capsaicin has been studied in various dermatological conditions and in other skin-related issues. Past studies documented that capsaicin plays a vital role in the prevention of atopic dermatitis as well as psoriasis. Moreover, TRPV1 is also very important for skin health because it acts as a capsaicin receptor. It is found in

nociceptive nerve fibers and nonneural structures. It prompts the release of a compound that is involved in communicating pain between the spinal cord nerves and other parts of the body. **Key Messages:** Here, we summarize the growing evidence for the beneficial role of capsaicin and TRPV1 and how they help in the relief of skin diseases such as inflammation, permeation, dysfunction, atopic dermatitis, and psoriasis and in pain amplification syndrome.

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Introduction

Background

Capsaicin, derived from the plants of the genus *Capsicum* [1], belongs to the Solanaceae family. It is the main pungent ingredient found in hot chili peppers. It is the most extensively consumed chili in all around the world. The domesticated species include *Capsicum annuum*, *Capsicum frutescens*, and *Capsicum chinense* [2]. The *Capsicum* genus is the only peppers plant that produces

Fig. 1. Chemical structure of capsaicin and capsaicinoids.

alkaloids carotenoids and flavonoids and capsaicinoids together. The first 2 categories of metabolites tend to be responsible for the attractive colors of the peppers ranging from green to red [3]. The capsaicinoids, however, attribute a taste characteristic known as pungency [4]. *Capsicum chinense* is the most pungent of them all [5]. Capsaicinoids are believed to have strong pharmacological properties that could be used in pain relief, weight reduction, cardiovascular conditions, and cancer prevention besides providing relief in gastrointestinal diseases. Capsaicin and other 14 homologs are identified as major active components of chili pepper [6]. Capsaicin and dihydro capsaicin are synthesized as main molecules.

Chemical Structure

Capsaicin was first purified in 1876 [7], but its structure was started to be explained in 1919 [8]. Now, the properties and structure of capsaicin are clarified (Fig. 1). Capsaicin has a nonpolar phenolic structure, and therefore it cannot be solubilized in water. Nonpolar solvents such as ether, benzene, dimethyl sulfoxide, and acetone are used to extract and maintain capsaicin properties. Ethanol can be also used as a solvent due to its mixed properties. According to its chemical structure, capsaicin can be well absorbed when administrated topically or orally, reaching up to 94% of absorption [9].

General Health Benefits of Capsaicin

The use of pepper is documented in several civilizations. They started cultivating it, and then brought it in their consumption due to its outstanding properties [10–13]. It got increasingly popular and well documented in 1600 BC. The fruit was used excitingly as pigments, food spices, and medicine [14,15]. At that time, it was used for stomach disorders and headaches [16]. Later, thereby, peppers are used in the industry as either dried powder (paprika) or oleoresin (extract of essential oil, waxes, carotenoids, flavonoids, and capsaicinoids). At the same time, it was also added to be an important application in food of military personnel [17].

Recent intensifying evidence suggests that capsaicin is advantageous in multifactorial metabolic disorders, cardiovascular diseases, obesity management, diabetes mellitus, cancers, dermatological conditions, and neurogenic bladder [18]. Capsaicin, besides this, also has a wide range of activities like analgesic, antipruritic, anti-inflammatory, antiapoptotic, antioxidant, and neuroprotective roles [19]. Especially, its use as an anti-inflammatory compound in psoriasis, brachioradial pruritus, aquagenic pruritus, notalgia paresthetica, nodular prurigo, and pruritus produced in patients on hemodialysis is worth mentioning [20]. Capsaicin is now available as a prescribed drug in many markets of countries for clinical indications for the treatment, especially for pain [21].

Capsaicin Synthesis

Capsaicin is synthesized by 2 diverse in vivo pathways: (i) synthesis of phenylpropanoids leading to aromatic ring construction and (ii) the other being by metabolism of the fatty acid chain foremost to the hydrophobic acyl chain addition to form capsaicinoids [22]. Besides the main capsaicinoid presence, capsaicin, many other similar molecules with reduced pungency and resiniferoids are identified from the *Capsicum* species. All these compounds, related to capsaicin, share therapeutic properties in pain and other pathophysiology illnesses [23].

Capsaicin Receptors

TRPV1 Receptor

In the last few decades, numerous unprecedented studies on the vanilloid receptor yielded the identification of many members in the transient receptor potential (TRP) family. These receptors regulate H^{1+} , Na^{1+} , Ca^{2+} , and Mg^{2+} intracellular concentrations [23]. The initial vanilloid receptor or VR1, later renamed as TRPV1, was identified in a subfamily [24]. The TRPV1 receptor is expressed in neurons and astrocytes, within the brain and spinal column, adipocytes, smooth muscle cells, vascular endothelial cells, hepatocytes, fibroblasts, various epithelia, T cells, and mast cells [25]. Capsaicin is shown to be attracted with high sensitivity and selectivity to the TRPV1 receptor. The receptor is sensitized with nanomolar concentrations ($EC_{50} = 99$ NM) which can be achieved after its ingestion orally which is followed by its high absorbability [26]. Capsaicin-related activation does not influence other TRP channels and the superfamily of the voltage-gated cation channel, including TRPV2–TRPV6. Capsaicin interaction with the TRPV1 receptor acts in a “tail-up, tail down configuration.” The tail interface is lured to the receptor through van der Waals forces. The head of the molecule interacts by hydrogen bonds between the vanillyl part and the amide neck at E⁵⁷¹ and T⁵⁵¹ residues of the TRPV1 channel correspondingly. Furthermore, the slip into the vanilloid pocket, Y⁵¹¹, G⁵⁷⁰, and I⁵⁶⁹ residues, plays major steric facilitations to fit the capsaicin molecule in the groove (Fig. 2) [27].

All TRP receptors comprise either K^{+} -selective channels with voltage-gated Ca^{2+} channels, voltage-regulated Na^{+} channels, cyclic nucleotide gradient channels, or lastly 2-pore channels. It should be reminisced that the TRPV1 receptor tends to be a nonselective cation channel that has more affinity toward Ca^{2+} than Na^{+} ions (P_{Ca}/P_{Na}). The

Fig. 2. a, b TRP helix structure. TRP, transient receptor potential.

TRPV receptors are divided into 3 groups with a gradient range of 0.1–20 [28]. In context to the spatiotemporal regulation of Ca^{2+} within the cell, there is a silent mechanistic second intracellular, message signal which is most of the time present in the animal kingdom [29]. The capsaicin antagonistic activity toward the TRPV1 receptor leads to variable efflux/influx pore size. This regulates the divalent and monovalent cation relativities in a frame of seconds to minutes. Phosphorylation of S⁸⁰⁰ of the TRPV1 protein by protein kinase C (PKC) increases permeability and enhances inward currents [30]. With the influx of Ca^{2+} , a cytosolic modulation occurs, by Ca^{2+} -binding proteins such as calmodulin (CaM). CaM specifically interacts conformationally to the binding domains on TRP channels [31]. Recent work on CaM showed that it binds to the cardiac ryanodine receptor (RyR2) (CaM-RyR2). This is again imperative to the Ca^{2+} release and contraction [32]. Nuclear accretion of CaM is believed to be a contributing factor in pathological cardiac hypertrophy [32].

TRPV1 Receptor Structure

TRPV-1 receptor is a homotetramer. The cryoelectron microscope studies revealed that the TRPV1 architecture is made of 4 subunits that are symmetrically organized

around the central conductive pore [33]. The heteromerization with other proteins is facing, however, an intense debate [34].

There are 28 such structures present in the TRPV1 structure [35]. The ankyrin repeats are the docking sites for the CaM protein. However, the carboxyl terminus, TRP helix, is assigned to a highly conserved helix that is used in its activation [36]. Specific capsaicin binding to TRPV1 is not yet elucidated nor illustrated in any form. Structural and architectural studies showed that the TRPV1 receptor is very similar to other voltage-gated H^+ , K^+ , Na^+ , Mg^{2+} , and Ca^{2+} channels [37]. The receptor exhibits a wide extracellular opening with a very short selective filter gate.

Substance P

The existence of TRPV1 in C-type peptidergic nociceptors is indicated by its colocalization with the main proinflammatory neuropeptides, calcitonin-gene-related peptide alpha (α CGRP) and substance P (SP) [38, 39]. SP and α CGRP play a vital role in the development and maintenance of neurogenic pain and inflammation as a genetic ablation of these peptides results in pain resistance [40–43]. All these neuropeptides are critically accumulated in large dense-core vesicles (LDCVs) and then released in response to proalgesic stimuli by a regulated, Ca^{2+} -dependent, and SNARE-mediated secretory pathway [44].

LDCVs can also work as carriers of a plethora of signaling molecules such as ion channels as well as receptors that might enable fast modulation of neuronal excitability [45]. This finding documenting the explosive hypothesis related to proalgesic recruitment of TRPV1 channels is a mechanism occurring in peptidergic nociceptors. A well-known proalgesic agent, ATP, is used to investigate the mechanisms underlying TRPV1 sensitization among sensory neurons [45–47]. Tominaga et al. [41] revealed that ATP-induced TRPV1 potentiation in peptidergic nociceptors specifically involves the exocytotic mobilization of new channels to the cell surface. Particularly, knockout of α CGRP expression inhibited the ATP-evoked TRPV1 delivery to the neuronal surface and prevented ATP-induced in vivo thermal hyperalgesia. Thus, algesic-induced exocytosis of TRPV1 channels in peptidergic nociceptors is a central mechanism in pain signaling [47].

Capsaicin Mechanism in Action

Several TRP channels are expressed in sensory endings of somatosensory neurons. These cells respond to both innocuous and noxious stimuli as discussed above. Their effect facilitates to open Ca^{2+} -permeable TRPA1, TRPV1, and TRPM3 nonselective channels. The depolarization evokes the potential firing and propagation to CNS pain signals [48]. The mechanism leads to local cytosolic Ca^{2+} rise that triggers neuropeptide release and causes neurogenic inflammation. Recent extensive research did not address its biological implications. Capsaicin-sensitive receptors are now shown to influence various CNS cells [49].

Structurally and functionally, the TRPV1 receptor is divided into 3 compartments: (a) capsaicin-induced neurons (sensory) in the peripheral nervous system, (b) central nervous system neurons, and (c) tissues of nonneuronal origin. The TRPV1 receptor is triggered through many stimuli which includes heat, capsaicin, protons ($pH < 5.9$), allicin and diallyl sulphides from garlic, gingerol from ginger, and piperine from black pepper. Toxic venoms of spider and jelly fish are also good agonists [50].

The first evidence of a selective action of capsaicin on C-polymodal nociceptors was obtained by the capsaicin-persuaded response of C-fibers at the saphenous nerve [51]. Capsaicin-conjured mechanical allodynia appears very much dependent on protein kinases, especially PKA and PKC, and other G-coupled proteins. The presence of substrate P – produced by incentive of capsaicin – increases intracellular Ca^{2+} levels through inhibition of both high-voltage- and low-voltage-activated T-type calcium channels. This selective inhibition primes up both primary and secondary effects of calcium influx that responds to delayed sensitization of the TRPV1 receptor [52]. The activation process is believed to be positively regulated by calcineurin, a specialized calcium-dependent CaM enzyme. Calcineurin is phosphorylated at T³⁷⁰ by PKA. This modification causes capsaicin-induced analgesia [53]. Involvement of other phosphorylations regulates increased trafficking and extracellular expressions. The NMDA receptor, for instance, is modified at S⁸⁹⁰, S⁸⁹⁷, and S⁸⁹⁶ that enhances its receptor activity. Similarly, modifications in the mitogen activated protein kinase (MAPK) pathway are linked to capsaicin activation where p38, an MAPK protein, is upregulated in the periphery and dorsal horns of the spinal cord [54].

CGRP Peptide

CGRP is a 37-amino acid peptide. The peptide exhibits 2 forms: α -CGRP and β -CGRP isoforms. β -CGRP, investigated less, differs by 3 amino acids which are predominantly expressed at the enteric sensory system encoded by a separate chromosome 11 region [61]. The *CGRP* gene is mainly controlled by expression of the MAPK signaling pathway and TNF α , COX-2, NO, and iNOS-induced cytokines [55].

The CGRP product is countenance in both central and peripheral neurons. It is a potent vasodilatory peptide which relates to nociception transmission. The peptide is released from neurons and various neurogenic inflammatory cellular cytokines which provide a defense mechanism [56]. Both CGRP (α and β) could be released by nonspecific stimuli in gastrointestinal tissues. Activation through capsaicin releases CGRP on the first stimuli. The second stimulus is effortless. This specific activation by high concentration of capsaicin releases only α -CGRP. β -CGRP is effective against neurons that are insensitive to TRPV1-capsaicin provocations [57].

From the recent literature, it is learned that activity associated with TRPV1 is the main transducer that links CGRP release. This activation causes local inflammation and sensitization of neuronal tissues related to pain. The human CGRP, specifically β -CGRP receptors, comprises 3 parts: receptor activity modifying protein 1, calcitonin-like receptor, and lastly receptor component protein.

The clinical use in rats demonstrated that capsaicin does not release substrate P from the trigeminal preparations which is responsible for neurogenic inflammation especially in humans. Instead, CGRP itself dilates the arterioles and then sensitizes neighboring sensory terminal nerve fibers. It is now clinically used in cluster headache or migraine which is exceptionally beneficial [57].

Skin Health and Capsaicin

A large number of studies pinpoint to the fact that stress-oriented changes could initiate or even aggravate various dermatological conditions. These changes include from skin cancer to inflammatory skin diseases such as acne, atopic dermatitis (AD), seborrheic eczema, psoriasis, prurigo nodularis, lichen planus, chronic urticaria, rosacea, and alopecia areata. In the skin, TRPV1 receptors are abundantly present in either neural or non-neural structures [54]. Whenever TRPV1 is activated, it helps to induce a second message through calcium (Ca²⁺)

influx in the epidermal keratinocytes. This entry of Ca²⁺ reduces inflammatory response one side, thereby decreasing harmful cutaneous stimulation. Capsaicin binding and induction, for the first time, desensitizes to the nervous system for burning sensation. The seminal studies illustrate fully that nociceptor activation releases pro-inflammatory neuropeptides [57].

Few studies have evaluated the clinical pharmacokinetics of orally administered capsaicin [58]. After an acute ingestion of 5 g of a capsaicin-rich hot pepper extract, a peak serum capsaicin level of 8.2 NM was observed after 45 min. After an hour later, capsaicin was no longer detectible, presumably owing to rapid hepatic metabolism [59]. In mice given a bolus dose of 10 mg/kg of capsaicin, far higher than that could be expected to be used in humans, the peak serum concentration was about 3 μ M; after 8 h, capsaicin was undetectable in the serum. It is therefore reasonable to expect that clinically tolerable intakes of capsaicin will achieve serum concentrations in the nanomolar range. Although capsaicin can inhibit certain voltage-sensitive calcium channels with an EC₅₀ of 5 μ M or higher [60, 61], it does not appear likely that this effect would be germane with feasible oral intakes of capsaicin in humans [61].

Dietary Capsaicin and Skin Dysfunction

The capsaicin-induced anti-inflammatory responses are proposed through the activation of the TRPV1 receptor. This activation causes the nerve endings to release proinflammatory neuropeptides, such as SP and CGRP [62]. The release of these important neuropeptides is activated by CGRP receptors and neurokinin 1. As a result, they lessen the dilation of vessels and increase vascular permeability. Neuropeptides which are released encourage degranulation of mast cells. Orientation of these cells increases the volume of capsaicin-induced neurogenic inflammation [63].

Skin Permeation

The use of capsaicin topically is found to be effective in management of other skin disorders, shingles, muscle strain, arthritis-related disorders, diabetic neuropathy, and pain disorders [64]. In an additional old study, Desai et al., [65] showed that capsaicin cream with 3 different concentrations (0.025, 0.5, and 1.0%) acts well on aquagenic pruritus patients. This is linked to the TRPV1 re-

ceptor and histamine-related itching [64]. Today, capsaicin oil-in-water nanoemulsions show complete successful results that enhanced skin permeation.

In a phase IV trial, comparison and efficacy of capsaicin in standard peripheral neuropathy treatment showed that 8% patch provided noninferior pain relief to pregabalin. Use of higher concentrations seems to produce transient adversative effects that include application site reaction, pain, pruritus, skin erythema, papules, and a transient increase in arterial blood pressure immediately after the application [64].

Skin Inflammation

In modern lifestyle, daily ups and downs create stress, which not only affects body systems but also their running physiology. Various studies in the last decade exhibit able evidence which shows that stress activity involves cutaneous neurogenic reaction [65, 66]. Inflammation of neurological tissues that are potentially involved in skin could progress as inflammatory dermatological diseases [67]. A small number of nano-based ethosomes, transfersomes, and cubosomes are available that could deliver capsaicin to the skin site. Nanoemulsions tend to produce advantageous results as they have small droplet size and high capsaicin load capacity and are easy to manufacture. These qualities produce higher permeability without skin vexation and relief to patients [68]. Ghiasi and colleagues [63] in a recent publication showed that, in rats, use of nanoemulsion/cream/gel, with a median droplet size of 13–14 nm, having prolonged 8-month stability, reduces skin inflammation edema within 2–3 h after application [68].

In a study of an antinociception therapeutic potential, it was shown that nociceptive nerve fibers tend to show sensitivity to capsaicin. Thereby, modulate activity of neurons increases SP releases from unmyelinated nerve endings of the skin, and later degranulation of cutaneous mast cells occurs [69]. A study on rats by Kim et al, [70] specified that use of siTNF α in assemblage with 2.5 mg of capsaicin nanoparticle encapsulation for 5 days yielded complete treatment of inflamed versus normal looking skin.

Permeability and anti-inflammatory effects of lornoxiclon in nanoemulsions (100–200 nm) are greatly increased. Use of aspirin- or capsaicin-derived nanoemulsion reveals excellent skin penetration and permeation which is proven by laser scanning microscopy analysis [70].

Atopic Dermatitis

AD is a skin-related inflammatory disease which is mostly seen among children. AD is a multiplex disease that has a genetic predisposition combined with an immune response as well as environmental factors [71]. Previous studies documented that various animal models have been developed for the investigation of AD [72]. A study was conducted by Back et al. [68] on a rat model; in this model, symptom development after weaning is followed by increases in the levels of serum IgE and skin NGF, IL-4, and IL-13 at approximately 3 weeks after injection [73]. In addition, this model also sides asthma-like airway inflammation [74]. Murakami et al. [71] indicated that symptoms of AD such as dermatitis and scratching behavior are persuaded by the neonatal injection of capsaicin [75]. Capsaicin triggers the cation channel TRPV1 and also revealed its antioxidant as well as anticancer effects. Moreover, in the recent treatment with the capsaicin analog, allergic reactions and AD symptoms were significantly reduced in NC/Nga mice [76]. Hiura [73] revealed that high doses of capsaicin seem to deploy different effects on the epidermis and neuronal system [77]. In addition, capsaicin frequently induces the death of TRPV-expressing dorsal root ganglion neurons. Apart from the existence of a 3-week lag period before the symptom development after capsaicin injection, the observations that cutaneous nerve fibers are lost, hair growth delayed, and skin NGF expression increased [73] suggest that changes in the internal milieu such as dysregulation of TRPV1-expressing cells, followed by compensatory events, may trigger symptom development.

Atopic skin is a condition that happens due to the disturbed epidermal differentiation and increased proliferation, triggering skin barrier dysfunction [71]. Moreover, at the molecular level, changes in many proteins have been investigated as possibly causative of AD development [78]. Among such changes, loss-of-function genetic mutations in the filaggrin gene strongly predispose to AD. In capsaicin-treated rats, filaggrin immunoreactivity was evident in both nonlesional skin and lesional skin. Filaggrin is defined as a large precursor protein that is subsequently proteolyzed into monomeric filaggrin in the stratum corneum [79]. Aberrant proteolytic processing of profilaggrin has been correlated with skin barrier dysfunction and AD development [80]. For the proper functioning of other skin barrier-related proteins such as corneodesmosin (CDSN), appropriate functioning of proteases is very important [81]. Furthermore, various proteases are also involved in CDSN and profilaggrin ac-

Fig. 3. Mechanism of capsaicin-evoked pain sensation. BoNTA, onabotulinum neurotoxin A; CGRP-R, calcitonin-gene-related peptide receptor complex; GEPANTs, CGRP receptor antagonists; mABs, monoclonal antibodies; TRPV1, transient receptor potential cation channel, subfamily V, member 1.

tivities. CDSN and profilaggrin directly cleave by the kallikrein (KLK)-related peptidases 5 and 7 [82, 83]. In addition, matriptase-, prostatic-, or Alox12b-knockout mice exhibit reduced profilaggrin cleavage in the epidermis [84–86], which is normally a rich source of proteases. Numerous proteases and protease inhibitors are expressed as epidermal keratinocytes differentiate [87]. These proteases are vital because of epidermal homeostasis; dysregulation of proteolytic pathways is now recognized as the mechanism underlying a growing number of skin diseases [87]. For instance, deficient matriptase activity causes severe skin barrier dysfunction and postnatal death [88]. Matriptase may be used to regulate intracellular ion homeostasis by controlling the epithelial sodium channel and the voltage-gated calcium channel, in turn regulating epidermal differentiation.

Psoriasis

Psoriasis is the most prevalent, chronic, inflammatory, and multisystem disease with primarily skin and joint manifestations that affects millions of people worldwide with a deleterious impact on their quality of life [89–93]. The term psoriasis, derived from the Greek word “psora,” can also be translated as “to itch” [94]. Itch in psoriasis

has often been underappreciated and accordingly often overlooked as a symptom requiring consideration in disease management [95, 96].

Among the most prevalent symptoms of psoriasis such as scaling, thickening of skin lesion, and redness, itch is not visible [90]. Historically, itch has been used to differentiate AD from psoriasis – the former being characterized pruritic, while the latter has often been considered nonpruritic. In addition, a recent meta-analysis of data from 22 clinical trials showed no significant difference in baseline itch between psoriasis and AD [97]. Previous studies demonstrated that itch is the most prevalent criterion for AD as well as a most important vital end point in AD studies [98, 99]. In addition, itch is recognized as the most oppressive symptom of psoriasis. Moreover, all psoriasis individuals are affected by itch [100–102]. Furthermore, itch with unfettered effect has an adverse impact on social, physical, and psychological well-being [95]. Besides this, there are several therapeutic options available for the treatment of psoriasis such as lesions on skin, but limited options are available for the management of itch symptoms because of incomplete understanding of psoriasis-associated itch [103–105]. Although itch is a very distressful symptom, guidance and management specifically for itch is not readily available (Fig. 3).

Conclusion

Capsaicin is derived from the family known as the vanilloid family. It binds with the TRPV1 receptor and performs its function. Capsaicin is stimulated by physical abrasion, heat, and also protons. It plays a vital role in the eradication of skin inflammation, psoriasis, and atopic dermatitis and overcoming chronic pain amplification syndrome. Inhibition of SP by capsaicin has been shown to significantly reduce itch in patients with psoriasis, supporting a potential role of this neuropeptide in the pathophysiology of psoriatic itch. Capsaicin dysregulates epidermal proteases such as matriptase and KLKs and alters profilaggrin and CDSN proteolysis, possibly explaining the observed skin manifestations. Such events may be influenced by the extent of postnatal epidermal development. Furthermore, the usage of capsaicin patch reduced pain by 71% compared to the other control site.

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