



Review

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ABSTRACT

Capsaicin is the active ingredient of chili peppers and gives them the characteristic pungent flavor. Understanding the actions of capsaicin led to the discovery of its receptor, transient receptor potential vanilloid subfamily member 1 (TRPV1). This receptor is found on key sensory afferents, and so the use of capsaicin to selectively activate pain afferents has been studied in animal and human models for various indications. Capsaicin is unique among naturally occurring irritant compounds because the initial neuronal excitation evoked by it is followed by a long-lasting refractory period, during which the previously excited neurons are no longer responsive to a broad range of stimuli. This process known as defunctionalisation has been exploited for therapeutic use of capsaicin in various painful conditions. We reviewed different studies on mechanisms of action of capsaicin and its utility in different clinical conditions. A beneficial role of capsaicin has been reported in obesity, cardiovascular and gastrointestinal conditions, various cancers, neurogenic bladder, and dermatologic conditions. Various theories have been put forth to explain these effects. Interestingly many of these pharmacological actions are TRPV1 independent. This review is aimed at providing an overview of these mechanisms and to also present literature which contradicts the proposed beneficial effects of capsaicin. Most of the literature comes from animal studies and since many of these mechanisms are poorly understood, more investigation is required in human subjects.

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1. Introduction

Capsaicin is the active ingredient of chili peppers obtained from the plants of genus *Capsicum*, the most heavily consumed chili in the world. Capsaicin and related compounds form a naturally occurring chemical group called capsaicinoids. Capsaicin gives the characteristic pungent flavor to chilies and is believed that these

chemicals are produced by the plant as a natural defense against herbivores and fungi. The effects of capsaicin on human body have been studied for more than a century. Hogeny in 1878 observed the burning sensation and hyperemia produced by an extract of *Capsicum* when applied on human skin (Toh et al., 1955). Later numerous animal studies revealed a fall in blood pressure, increase in salivary and gastric secretion and increased intestinal activity after an intravenous injection of *Capsicum* extract (de Lille and Ramirez, 1935; Nast, 1923). As a result, capsaicin has been an exciting pharmacological agent and its utility in different clinical conditions is being explored.

We aim to provide a review of the pharmacological properties of capsaicin and the mechanisms behind it. We identified references for this review by searching MEDLINE, EMBASE and CINAHL electronic databases through August, 2013. Keywords and MeSH terms like “capsaicin”, “clinical uses”, “pain”, “obesity”, and “transient receptor potential vanilloid subfamily member 1” were used. We also hand searched related articles in these electronic databases. To make the review comprehensive, we considered articles published in non-english language as well. The reference list was compiled based on their relevance to the broad scope of this review.

2. Chemistry of capsaicin molecule

Capsaicin (*trans*-8-methyl-*N*-vanillyl-6-nonenamide) is a naturally occurring alkaloid derived from plants of the genus *Capsicum*, better known as chili pepper fruit. The molecular formula for capsaicin is $C_{18}H_{27}NO_3$. It is a highly volatile, pungent, hydrophobic, colorless and odorless white crystalline powder. It is synthesized in the chili pepper by addition of a branched-chain fatty acid to vanillylamine (Fujiwaka et al., 1980). Commercially it is manufactured by the reaction of vanillylamine with 7-methyloct-5-ene-1-carboxylic acid chloride or isolated from paprika or obtained by grinding dried ripe fruits of *Capsicum frutescens* L. (chili peppers) into a fine powder. The formulation types registered are dry powder, liquid formulation and liquid spray ground. Capsaicin is believed to be metabolized by dehydrogenation, producing unique macrocyclic, -diene, and -imide metabolites. The metabolism was shown to be catalyzed by enzymes cytochrome P 1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 (Reilly et al., 2003).

3. Pharmacological actions of capsaicin

3.1. Pain relief

Transient receptor potential vanilloid 1 receptor (TRPV1), also known as the capsaicin receptor, is part of the transient release potential (TRP) ion channel family which helps the body in sensing heat or warmth (Ramsey et al., 2006). After its cloning in the year 1997 from a rat dorsal root ganglia, TRPV1 was investigated for a rather widespread distribution in rat and human brain. Mezey et al. (2000) performed immunocytochemistry and in situ hybridization histochemistry using specific ribonucleic acid (RNA) probe to localize TRPV1 expressing cells in the rat brain, later confirmed by reverse transcription-polymerase chain reaction (RT-PCR). RT-PCR verified the expression of TRPV1 messenger RNA in rat cortex, hippocampus, and hypothalamus. This was followed by numerous investigators detecting TRPV1 expression in the cortex, hippocampus, dentate gyrus, central amygdala, striatum, hypothalamus, thalamus, cerebellum, locus ceruleus, cochlear nuclei, nucleus of the trigeminal nerve and inferior olive (Cristino et al., 2006; Starowicz et al., 2008).

Evidence of TRPV1 involvement in pain perception was presented by Giordano et al. (2012) who showed that the prelimbic and infralimbic cortex undergoes several changes following neuropathic pain, including enhanced TRPV1 expression on glutamatergic fibers and excitatory signaling by basolateral amygdala-medial prefrontal cortex (mPFC) neurons, with subsequently increased extracellular levels of glutamate. This contributes to the processing of noxious stimuli. Furthermore, N-arachidonoyl-serotonin, which is a hybrid TRPV1 antagonist and fatty acid amide hydrolase inhibitor, normalized the imbalance between excitatory and inhibitory responses in the mPFC neurons, resulting in pain inhibition (de Novellis et al., 2011). Capsaicin is an agonist of TRPV1 and reduces its heat activation threshold (Knotkova et al., 2008). TRPV1 is activated via phosphorylation by protein kinases, the calcium and calmodulin-dependent protein kinase II (CaMK II kinase) and cleavage of phosphatidylinositol 4,5-bisphosphate (PIP2) by phospholipase C (Mohapatra and Nau, 2003; Premkumar and Ahern, 2000; Vellani et al., 2001). The N-terminus of TRPV1 has several phosphorylation sites for protein kinases which aid in its activation (Caterina et al., 1997) whereas TRPV1 desensitization results from its dephosphorylation by phosphatases (Ma and Quirion, 2007). Capsaicin activated TRPV1 goes into a long refractory state and thus a previously excited neuron is resistant to various stimuli ranging from mechanical pressure to endo/exogenous pain and proinflammatory agents (Szallasi and Blumberg, 1999). At the molecular level, this results from extracellular calcium dependent conformational changes in the receptor protein, ultimately closing the channel pore (Liu and Simon, 1996). However, this effect may be temporary and therefore may not account for a persistent pain relief seen clinically.

Upon excitation, TRPV1 releases sensory neuropeptides, which are dependent on capsaicin concentration used (JM, 1996) but then also prevent the restoration of the neuropeptides by blocking axoplasmic transport of substance P and somatostatin in sensory neurons (Gamse et al., 1982), thereby depleting neuropeptides. This was thought to be primarily responsible for pain relief, but capsaicin appears to provide analgesia by a cascade of events resulting in “defunctionalization” of the nociceptive fibers rather than just by depleting the neuropeptides (Anand and Bley, 2011). Defunctionalization may include loss of membrane potential, depletion of neuropeptides, inability to transport neurotrophic factors, and reversible retraction of epidermal and dermal nerve fiber terminals (Anand and Bley, 2011). Calcium overload may result in a loss of mitochondrial function and inhibition of metabolism may disrupt the plasma membrane integrity, causing the nerve ending to collapse (Anand and Bley, 2011). Therefore, defunctionalization of the afferent neurons by stimulation of TRPV1 causes long term functional and phenotypic alterations in the whole neuron.

While capsaicin has been shown to damage the sensory nerve endings (Anon, 2007; Chard et al., 1995), repeated topical application of capsaicin also results in degeneration of the cutaneous autonomic nerve fibers, decreasing the pain sensation (Nolano et al., 1999; Simone and Ochoa, 1991). Although not clearly understood but TRPV1 mediated calcium influx and glutamate release have been thought to be responsible for it (Sikand and Premkumar, 2007). Resiniferatoxin (RTX), a potent analog of capsaicin, has been shown to cause loss of unmyelinated nerve fibers and detectable levels of damage to myelinated ones as well in adult rats, showing that RTX reduces thermal pain perception by depleting neurons that express TRPV1 (Pan et al., 2003).

For pain relief, capsaicin has been approved by the US Food and Drug Administration as an 8% dermal patch. Each patch has synthetic capsaicin 640 mcg/cm² with total dose of 179 mg in one patch (Qutenza, 2013). A low dose application (0.075% cream and 0.025% gel) has shown no clinical use in pain reduction (Derry and Moore, 2012; Kulkarni et al., 2013). There have been

numerous clinical trials which studied the analgesic effect of capsaicin in humans (Anon, 2013). A recently published prospective observational study shows 8% capsaicin patch is safe and effective in controlling neuropathic pain resulting from post-herpetic neuralgia, post-surgical neuralgia, post-traumatic-neuropathy, polyneuropathy and mixed pain syndrome (Maihofner and Heskamp, 2013). There was marked improvement in pain attacks, sleep duration and quality with decreased dependence on opioids and anti-epileptics. Around 10% of the patients studied reported adverse drug reactions, amongst which erythema and pain at the application site were the most common. Simpson et al. (2013) showed that repeated applications of 8% capsaicin patch in painful HIV-associated distal sensory polyneuropathy (HIV-DSP) were well tolerated and resulted in 22–27% mean percentage decrease in Numeric Pain Rating Scale (NPRS). Additionally, integrated results of two phase-3, randomized controlled trials showed that 8% capsaicin patch was effective regardless of gender, baseline pain score, duration of HIV-DSP, or use of concomitant neuropathic pain medication and a single 30 min patch application provides significant ($p=0.002$) pain relief for 12 weeks (Brown et al., 2013). Adlea, a highly purified form of capsaicin, is currently under investigation for its analgesic properties. It reportedly reduced pain in conditions like intermetatarsal neuromas (Diamond and Miller, 2006), lateral epicondylitis (Richards et al., 2006) and end stage osteoarthritis (Cantillon et al., 2005), as compared to placebo. The results of phase-3 trials studying the safety and efficacy of this drug in patients undergoing total knee arthroplasty are awaited.

Palvanil (N-palmitoyl-vanillamide) is a non-pungent capsaicin-like compound, found in low amounts in Capsicum. It produced significantly less fluctuations in body temperature and bronchoconstriction, when administered systemically at analgesic doses, as compared to capsaicin (Luongo et al., 2012). These TRPV1 mediated analgesic and anti-inflammatory effects were observed in neuropathic mice. Palvanil exhibits a slower kinetics of TRPV1 activation and desensitized TRPV1 with significantly higher potency than capsaicin (De Petrocellis et al., 2011).

3.2. Weight reduction

TRPV1 activation results in recruitment of catecholaminergic neurons in the rostral ventrolateral medulla of the brain (Akabori et al., 2007). This release of catecholamine has been attributed to some of the weight modifying effects of capsaicin. The human study conducted by Yoshioka et al. (1995, 1998) showed an increase in diet-induced-thermogenesis and lipid oxidation when high fat diet is mixed with capsaicin. Subsequently, an increase in energy expenditure after capsaicin intake was supported by studies by various investigators (Josse et al., 2010; Lee et al., 2010; Lejeune et al., 2003; Ludy and Mattes, 2011). Among these studies, an increase in lipid oxidation was reported by Lejeune et al., Josse et al. and Lee et al. and a decrease in appetite was reported in a study by Ludy and Mattes. Topical application of capsaicin has shown to increase the expression of adiponectin and other adipokines, thus reducing fat accumulation in the adipose tissue of obese mice (Lee et al., 2013). In stark contrast, no effect of capsaicin on energy expenditure or lipid oxidation was shown in studies by Smeets and Westerterp-Plantenga (2009) and Galgani et al. (2010).

Obesity related diseases like insulin resistance and type 2 diabetes mellitus are marked by dysregulations in glucose and lipid levels. 0.015% Capsaicin supplement to genetically obese mice fed on high fat diet resulted in decreased fasting glucose and plasma triglyceride levels (Kang et al., 2011). Kang et al. (2010) demonstrated that dietary capsaicin reduced obesity-induced glucose intolerance by not only suppressing inflammatory responses but

also enhancing fatty acid oxidation in adipose tissue and/or liver, both of which are important peripheral tissues affecting insulin resistance. Similar deductions were recently made by Lee et al. (2013) (topical, 0.075% capsaicin) and by Okumura et al. (2012) (dietary, 0.0042% capsaicin) in obese mice.

3.3. Anti-cancer properties

In last couple of decades, a lot of evidence has emerged trying to establish the anti-cancer properties of capsaicin. Researchers from around the world have demonstrated anti-cancer properties of capsaicin in specific carcinogenic molecules and many theories have been put forth to explain this behavior. It appears that anti-cancer effects of capsaicin are not mediated through interaction with TRPV1 receptors (Raisinghani et al., 2005) but still there is some evidences which show TRPV1 mediated increase in intracellular calcium, initiating the apoptotic cascade (Ziglioli et al., 2009). Lin et al. (2013) studied the effect of capsaicin on human cancer cell line derived from an immortal cell line primarily used for research purposes. They reported effects like reduced proliferation and viability of cancer cells, arrest of cell cycle at G₂/M phase and loss of mitochondrial membrane potential resulting in activation of caspase 9, which in turn is responsible for cell apoptosis. Loss of mitochondrial membrane potential, leading to apoptosis, was also shown in a study by Pramanik et al. (2011), which demonstrated capsaicin induced apoptosis in pancreatic cancer cells. They also showed that capsaicin inhibited the enzymatic activity of superoxide dismutase, catalase and glutathione peroxidase. In addition, they demonstrated capsaicin induced inhibition of electron transport chain complexes 1 and 3 in cancer cells, with no effect on normal cells. The inhibition of complexes 1 and 3 results in the generation of reactive oxygen species which are lethal to human cells. Recent evidence in pancreatic cancer cells by Zhang et al. (2013) showed that capsaicin induced cell arrest in G₀/G₁ phase, up regulated caspase-3 and decreased viability of cancer cells in a dose dependent manner. Another line of evidence was presented by Mori et al. (2006) in which they studied the effect of capsaicin on prostatic cancer cell lines and showed that capsaicin inhibits nuclear factor-kappa (NF- κ) and tumor necrosis factor-alpha (TNF- α) activation. Similar evidence of anti-cancer effect has been shown in numerous cancerous conditions like gastric cancer (Huh et al., 2011; Wang et al., 2011), colon cancer (Lu et al., 2010), breast cancer (Chang et al., 2011; de-Sa-Junior et al., 2013), lung cancer (Anandakumar et al., 2012), leukemia (Tsou et al., 2006), and hepatocellular carcinoma (Moon et al., 2012).

Contrary to the compelling evidence provided by the studies cited above, some reports have shown an increased rate of carcinogenesis with the use of capsaicin. Data published in 1951 suggests the development of neoplastic changes in rat liver after capsaicin ingestion (Hoch-Ligeti, 1951). A recent evidence comes from Liu et al. (2012) in which the authors show the up-regulation of tumor associated nicotinamide adenine dinucleotide (NADH) oxidase expression in human colon carcinoma cells, associated with tumor cell proliferation and migration. Similarly, increased risk of gastric cancer has been reported in studies from India, Spain, Mexico and Korea (Lopez-Carrillo et al., 2012). Bode and Dong (2011) reported that prolonged suppression of TRPV1 results in increased risk of skin cancer. Studies by Gannett et al. (1990), and Lee and Kumar (1980) have shown that capsaicin is metabolized by cytochrome P450 to aromatic and aliphatic hydroxylated products (Surh and Lee, 1995) and many new reactive metabolites were subsequently identified by Reilly et al. (2003). These by-products of capsaicin's metabolism may be responsible for its carcinogenic properties. In addition, Yang et al. (2013) showed that low concentration of capsaicin enhanced migratory and invasive

capabilities of colorectal cancer cells. They also showed the upregulation of matrix metalloproteinase-2/-9 in colorectal cancer cells which promoted cancer metastasis.

3.4. Cardiovascular effects

TRPV1 is distributed in the sensory nerves in the cardiovascular structures, near the epicardium (Zahner et al., 2003) and in vascular endothelial cells (Poblete et al., 2005). Reduced blood flow to myocardium (during myocardial infarction) results in the release of free oxygen radicals which directly activate TRPV1 (Huang et al., 1995; Schultz and Ustinova, 1998). TRPV1 has been shown to be involved in sensing chest pain resulting from myocardial infarction as well (Pan and Chen, 2004; Steagall et al., 2012). Recent studies in infant rat models suggest the same (Ide et al., 2012). TRPV1 has been linked to cardio-protective effects as well. Peripheral nociception results in non-ischemic cardio-protection through TRPV1 (Jones et al., 2009). Wang and Wang (2005) presented compelling evidence linking TRPV1 with infarct size. In their experiment TRPV1-knockout mice had larger infarct sizes. TRPV1's protective effect against myocardial ischemic/reperfusion injury was noted by Sexton et al. (2007) who postulated that 12-hydroperoxyeicosatetraenoic acid, a 12-lipoxygenase arachidonic acid metabolite, is an endogenous ligand for TRPV1 and this pathway is up-regulated locally during myocardial injury.

As noted above, TRPV1 is distributed along the vascular system and is involved in vascular autoregulation, resulting in vasoconstriction as well as vasodilatation, depending on the physiological state. TRPV1 activation results in the release of substance P, a neurokinin, which binds to neurokinin 1 (NK1) receptor resulting in vasoconstriction. Vasodilatory effects result from both neuronal and vascular mechanisms of TRPV1 activation. Sensory neurons have TRPV1 which, upon activation, release calcitonin gene-related peptide (CGRP), resulting in vasodilatation (Zygmunt et al., 1999). As for the vascular mechanism, TRPV1 activation results in the release of protein kinase A and epithelial nitric oxide synthase, which releases nitric oxide, resulting in vasodilatation (Yang et al., 2010). Both the mechanisms mediate through increased intracellular calcium. This was supported very recently by Chen et al. (2013), who demonstrated vasodilatory effects of capsaicin on rat mesenteric artery.

Additionally, capsaicin has been shown to inhibit platelet aggregation (Adams et al., 2009; Mittelstadt et al., 2012; Raghavendra and Naidu, 2009; Sylvester and LaHann, 1989). The anti-aggregating effect of capsaicin on platelets has been postulated to be independent of TRPV1 activation. Meddings et al. (1991) proposed that capsaicin induced alteration in the fluidity of platelet membrane, later confirmed by Aranda et al. (1995). The TRPV1-independent anti-platelet aggregating effect of capsaicin was recently demonstrated by Mittelstadt et al. (2012), who showed that a selective competitive TRPV1 inhibitor A-993610 had no effect on the ability of capsaicin to inhibit platelets. However, Harper et al. (2009) provided conflicting data and showed the pro-aggregating effects of capsaicin and demonstrated that the effect was TRPV1 dependent. The authors proposed that capsaicin, through TRPV1 dependent serotonin release, contributed to adenosine diphosphate and thrombin induced platelet activation.

3.5. Gastrointestinal effects

Ward et al. (2003) established TRPV1 activity on nerves within the myenteric ganglia and interganglionic fiber tract throughout the GI tract, muscle layers, blood vessels and mucosa within the GI wall of mice, rats and guinea pigs. TRPV1 is expressed in

non-nervous tissues like gastric epithelial cells as well and stimulate the secretion of gastrin (Ericson et al., 2009). Gastrointestinal effects of capsaicin are dose dependent. Evidence supporting beneficial as well as detrimental effects of capsaicin is present. Activated TRPV1 releases CGRP and activates cyclooxygenase-1 enzymes, which have gastroprotective effects (Ohno et al., 2008; Saeki et al., 2004). Additionally, capsaicin has shown to alter brush border membrane permeability, associated with increased microvilli length and perimeter, resulting in increased absorptive surface of small intestine in rats (Prakash and Srinivasan, 2010). This was supported by similar findings by the same authors few years later, who showed increased zinc absorption in rats fed on capsaicin (Prakash and Srinivasan, 2013). Chronic dietary capsaicin had beneficial effects in non-alcoholic fatty liver disease by promoting hepatic phosphorylated hormone-sensitive lipase (phosphor-HSL), carnitine palmitotransferase 1 (CPT1) and peroxisome proliferator-activated receptor δ (PPAR δ) (Li et al., 2013).

Detrimental effects on GI tract on prolonged exposure of high doses of capsaicin have also been reported (Wang et al., 2005). Substance P released from activated TRPV1 has been mediated in the inflammation of GI tract (McVey and Vigna, 2001; Pothoulakis et al., 1994). There is an increased TRPV1 expression in irritable bowel syndrome (IBS), which also contributes to visceral hypersensitivity and pain in IBS (Akbar et al., 2008). Similar evidence was provided by Holzer (2008), Li and Duan (2011) and Akbar et al. (2010).

3.6. Neurogenic bladder

TRPV1 receptors are densely distributed in the urinary tract (Yiangou et al., 2001) but patients with neurogenic bladders have an increased expression of TRPV1 as shown by increased immunoreactivity in experiments conducted by Brady et al. (2004). It is known that TRPV1 receptors are important in the pathogenesis of overactive bladder diseases and its modulation can reduce the symptoms. Mice lacking the TRPV1 channels have altered micturition thresholds suggesting that TRPV1 channels may play a role in the detection of bladder filling (Daly et al., 2007). Intravesical capsaicin application induces detrusor contractions and reduces the bladder volume threshold to reflex micturition in humans (Cruz et al., 1997). In addition, capsaicin-sensitive bladder afferents contribute to the decrease of the volume threshold to reflex micturition found in experimental animals subjected to bladder inflammation (Lecci et al., 1998). TRPV1 plays an important role in the pathogenesis of detrusor overactivity and can be a useful alternative to standard anti-cholinergic therapy but it should be noted that capsaicin is an irritant when instilled intravesically and therefore its utility is still uncertain. Resiniferatoxin, a potent TRPV1 agonist, has shown promising results in providing relief in painful bladder syndrome but its role in hyperactive bladder remains unclear.

3.7. Dermatological conditions

Recently, TRPV1 receptors have been demonstrated on human keratinocytes, and the activation of epidermal TRPV1 has been shown to induce the release of pro-inflammatory mediators (Li et al., 2007). Hypoxia-inducible factor-1 α (HIF-1 α) is an important factor in psoriatic epidermal proliferation and HIF-1 α gene translocation in psoriatic epidermis was downregulated after capsaicin treatment for 21 days (Yu, 2011). Topical application of 0.025% capsaicin was shown to exert a moderately suppressive effect on histamine, substance P and proteinase activated receptor-2 mediated itch (Sekine et al., 2012). In contrast, trials conducted to study the effect of topical capsaicin on hemodialysis induced

pruritis, idiopathic intractable pruritis and nostalgia paresthetica failed to provide any convincing evidence (Gooding et al., 2010). Also, an animal study by Back et al. (2012) revealed that 50 mg/kg subcutaneous capsaicin resulted in the development of chronically relapsing pruritic dermatitis which mediated through increase in the number of mast cells and hyperproduction of serum immunoglobulin E.

4. Capsaicin analogs

CH-19 Sweet is a non-pungent variety of chili peppers, which has three forms of capsaicin analogs – called capsate, dihydro-capsate and nordihydrocapsate (Sasahara et al., 2010). These analogs were shown to be TRPV1 agonists, less pungent than capsaicin and enhance energy consumption through activation of the sympathetic nervous system. Because of a minor variation in their chemical structure, like the presence of an ester bond instead of an amide bond between the vanillyl group and the fatty acid chain, capsate is hydrolyzed as it crosses the oral mucosa, making it non-pungent to taste (Ludy et al., 2012). But capsates have

shown equal potency to activate TRPV1 in the gut resulting in similar sympathetic nervous system activation (Snitker et al., 2009).

5. Areas of future research

A new evidence supporting the use of capsaicin in a variety of clinical situations has been identified (Table 1). But these applications of capsaicin have not been well-researched. Moreover, the analgesic properties of capsaicin need to be investigated in other painful conditions like kidney stones, appendicitis, gout, giant cell arteritis, chronic pancreatitis, tension headache, dysmenorrhea, peripheral vascular disease and many more. The current literature, at large, lacks multicenter, randomised, double blinded and controlled studies in humans, which can establish the safety and efficacy of capsaicin in numerous clinical situations described in this review. Additionally, capsaicin has been known to play a definitive role in the management of conditions like oral mucositis, migraine and rhinopathy (Hautkappe et al., 1998) but we could not identify enough number of related articles in our search, which we could comment on and include in this review. Effectiveness of capsaicin in these conditions will form the areas of future research.

Table 1
Emerging evidence of important pharmacological actions of capsaicin.

Conditions	References
Superficial punctate keratopathy	Kagawa et al. (2013)
Asthma	Rehman et al. (2013)
Labor pains and delivery	Mirza et al. (2013)
Alzheimer's disease	Jiang et al. (2013)
Promoting skeletal muscle hypertrophy	Ito et al. (2013)
Fibromyalgia	Casanueva et al. (2013)
Reduced minimum inhibitory concentration (MIC) of ciprofloxacin	Kalia et al. (2012)
Cluster headaches	Saper et al. (2002)

Table 2
Unclear properties of capsaicin in different physiological systems.

Role of capsaicin	Mode of administration	Beneficial effects	Detrimental/no effect
Pain	High dose (8%) dermal patch	Reduces neuropathic pain (Maihofner and Heskamp, 2013)	Enhanced sensitivity to noxious stimuli, capsaicin-induced dermal pain (Bode and Dong, 2011)
Body weight	Dietary	Diet induced thermogenesis and lipid oxidation (Yoshioka et al., 1995; 1998), increased lipid oxidation (Josse et al., 2010; Lee et al., 2010; Lejeune et al., 2003), decrease in appetite (Ludy and Mattes, 2011), and decreased triglyceride level in genetically obese mice (Kang et al., 2011)	No effect on energy expenditure or lipid oxidation seen (Galgani et al., 2010; Smeets and Westerterp-Plantenga, 2009)
Cancer	Dietary	Anti-cancer effects in cancers in pancreas (Zhang et al., 2013), gastric (Wang et al., 2011), colon (Lu et al., 2010), breast (de-Sa-Junior et al., 2013), prostate (Mori et al., 2006), lung (Anandakumar et al., 2012), leukemia (Tsou et al., 2006), and hepatocellular carcinoma (Moon et al., 2012)	Increased rate of carcinogenesis seen in: rat liver (Hoch-Ligeti, 1951), gastric cancer (Lopez-Carrillo et al., 2012), skin cancer (Bode and Dong, 2011), and colorectal (Yang et al., 2013)
Cardiovascular system	Dietary	Smaller infarct sizes (Wang and Wang, 2005), protective against reperfusion injury (Sexton et al., 2007), and platelet anti-aggregating effect (Adams et al., 2009; Mittelstadt et al., 2012; Raghavendra and Naidu, 2009; Sylvester and LaHann, 1989)	Platelet pro-aggregating effects (Harper et al., 2009)
Gastrointestinal system	Dietary	Increased absorptive surface of small intestine in rats (Prakash and Srinivasan, 2010)	TRPV1 mediates the inflammation of the GI tract (Pothoulakis et al., 1994)
Urinary bladder	Intravesicle instillation	Painful bladder syndrome, hyperactive bladder (Cruz et al., 1997)	Capsaicin is irritant when instilled intravesically (Li et al., 2007)
Dermatological conditions	Topical	Psoriasis (Yu, 2011), and histamine mediated itch (Sekine et al., 2012)	No benefit seen in hemodialysis induced pruritis, and idiopathic pruritis (Gooding et al., 2010)

6. Conclusion

The clinical applications of capsaicin are restricted to pain management. A part of this can be attributed to the lack of specificity in action and associated toxicity. Furthermore, capsaicin has limited applicability in other indications because of the conflicting data as summarized in Table 2. More experiments are required to study the interaction of capsaicin with TRPV1 receptors which might reveal more pharmacological properties. Experiments are underway to modify the capsaicin molecule to overcome some of the adverse effects, mainly its pungency and chili taste.

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