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REVIEW ARTICLE: TRANSIENT RECEPTOR POTENTIAL VANILLOID 1 (TRPV-1): IT'S ROLE IN WOUND HEALING

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ABSTRACT

This review paper is about TRPV1(transient receptor potential vanilloid 1) which play a key role in healing of wounds and other diseases. A wound is an impairment of the integrity of the skin because of physical harm or disease. TRPV1 tends to mediate sensory transduction as a polymodal receptor triggered by host stimuli. The physiological or pathological effects of non-neuronal TRPV1 have been implicated in inflammation and immunity, cardiovascular system and diseases such as obesity. Up to six orally active TRPV1 antagonist molecule are currently undergoing clinical research.

***Keywords*:** TRPV1, wound healing, vanilloid receptor, TRP families, polymodal receptor.

Introduction

A wound is an impairment to the integrity of the skin due to physical damage or illness (Cullum *et al*., 2016). In general, a wound involves "tissue disruption with consecutive loss of function of the normal anatomical structure"(Bickers, 1967). Wounds can occur due to any injury, disease state or insect bite or abrasions. It may be deeper, spreading to subcutaneous tissue, destroying other tissues such as tendons, muscle, nerves, parenchymal organ and also bone structure. Wounds may emerge from pathological processes within the involved organ that begin externally or internally (Velnar *et al*., 2009). There are multiple types of wound injuries including acute and chronic wounds. The most common observed cases include ulcerative wounds and diabetic wounds. Surgical wounds are also seen commonly (Nicky Cullum). About 15% of all patients with diabetes are at the risk of foot ulcers during their lifetime and it is estimated that 70% of treated ulcers recur within the 5 years. The key risk factors for developing diabetic foot ulcers are peripheral neuropathy, peripheral vascular diseases, abnormal plantar pressure load and infection (Beckert *et al*., 2006).

The process of wound healing includes multiple stages like haemostasis/inflammation, the phase of proliferation and the phase of remodelling. The sub-endothelium, collagen and tissue factor exposure can cause platelet aggregation after skin injury, which results in degranulation and release chemotactic factors and growth factors to form clots. Neutrophils the first cell to appear at the injury site for cleaning the debris and bacteria to provide a good environment for wound healing (Wang *et al*., 2018). All four phases of wound healing process must occur in correct sequence and time period for a wound to heal successfully. There are several variables that can affect wound healing that interfere with one or more stages, causing improper or damage repair of tissue (Velnar *et al*., 2009). The variables that affect the repair can be classified into local and systemic influences. Local variables are those that specifically influence the characteristics of the wound itself, such as oxygenation, infection, foreign body, venous sufficiency while Systemic variables affect the individual's overall health or disease status that influence his or her ability to recover such as age and gender, sex hormones, stress, ischemia and obesity (Guo & DiPietro, 2010).

Currently a wide range of topical antibiotics, antifungal and antiseptic drugs are used for treatment of wound infections. other than these new effective techniques such as tissue engineered growth technique, recombinant growth factor techniques and silver dressings are also used nowadays for treatment of wound infections (Lipsky and Hoey, 2009).

Wound repair involves the integration of interdependent processes and signals, including soluble mediators, inflammatory cytokines formed by a variety of types of cells, cell proliferation and migration, and extracellular matrix component production, among others. There are many receptors involve in the healing of wounds. PPAR receptor play a wide role in skin wound healing. Peroxisome proliferator-activated receptor control many cellular and metabolic processes. These receptors are involved in the treatment of chronic diseases such as diabetes, obesity and new skin wound healing function (Wahli, 2002). Skin wound healing is a complex and highly regulated healing process. Cellular, humoral and molecular process start immediately after injury and can last for years (Reinke & Sorg, 2012).

In normal individual and those suffering from chronic wounds, the adenosine A2A receptor is also a novel way to improve wound healing and angiogenesis. Adenosine, a potent endogenous physiological mediator, controls a large

spectrum of physiological processes. The topical use of adenosine A1 while A2A receptor agonists encourage the healing of full thickness dermal wounds (Montesinos *et al*., 2003). The role of TRPV1 mediated calcium- dependent inactivation on orai1 in cell migration and wound healing (Bastián-Eugenio *et al*., 2019). TRPV1 receptors may be activated by cannabidiol, a CBI receptor agonist, promoting neurotransmission of glutamate and anxiety responses (Campos & Guimarães, 2009).

The other receptor is also involved in process of healing. The absence or blockage of this vanilloid subtype 1 transient receptor potential (TRPV1) ion channel receptor affects the healing of epithelial injury. Transient receptor potential (TRP) channels are polymodal receptors that are activated by multiple external and endogenous stimuli. The TRP superfamily is composed of 28 different genes that are subdivided into seven different subfamilies with different variable permeability. The activation of TRPV1 allegedly causes the release from the sensory nerves of tachykinin neuropeptides (e.g., substance P, neurokinin A, and calcitonin gene related peptide), causing neurogenic inflammation. The signal from the TRPV1 is involved in proliferation of cells and single epithelial cell migration (Sumioka *et al*., 2014).The present review article summarizes the role of TRPV1 in the wound healing process.

Review of Literature

There are different phases of wound healing process that involves haemostasis and proliferation followed by remodelling. These phases are briefly described as follow:

Haemostasis/inflammation phase: - it often takes 72 h to complete. Proliferative phase: - There is accumulation of cells and profuse connective tissue. Cytokinin and growth factors are recruited at the site of injury TGF-BETA1, TGF-BETA2, TGF-BETA3, interleukin (IL) and angiogenesis factors, such as transforming growth factor-beta family. This phase last for days or weeks. Remodelling phase: - Here a precise equilibrium exists between established cell apoptosis and new cells development. Any abnormality in this phase may lead to excessive wound healing (Wang *et al*., 2018).

Pathogenesis of wound healing

Excessive wound healing is caused by skin injury, which include trauma, insect bit, bums, surgery, vaccinations and infections. After the injury to skin, the inflammatory process begins to initiate wound healing. Excessive wound healing often involves an exaggerated function of fibroblast and accumulation of ECM during wound healing. There are two forms of excessive wound healing are keloid and hypertrophic scar. "keloid" means strongly inflamed pathological process and "hypertrophic scar "means more weakly inflamed pathological process(Adcock, 2009). In several physiological processes, cell migration plays a fundamental role, including wound healing, cancer growth and inflammation (Waning *et al*., 2007).

Transient receptor potential vanilloid subfamily member 1

Transient receptor potential vanilloid subfamily member 1(TRPV1), the subtype of transient receptor potential (TRP) family, is a non-selective cation channel that can allow passage of hydrogen, sodium, calcium and magnesium. Activation of TRPV1 also contributes to release of tachykinin neuropeptides, neurokinin A and calcitonin gene related peptides from the sensory nerves (Zhang *et al*., 2019). The TRP superfamily is composed of 28 different genes that are subdivided into seven different subfamilies (TRPA, TRPC, TRPM, TRPML, TRPN, TRPPAND TRPV) Each of them possesses variable cation permeability (Huang *et al*., 2008). The TRPV1 channel is involved in calcium signalling regulation and essential for many cellular processes including proliferation, apoptosis and activation of T cells. TRPV1 appears as a polymodal receptor that are activated by host of stimuli to mediate sensory transduction (Por *et al*., 2016). In the development of many diseases, TRP channels play a significant role. The cation channel also known as capsaicin receptor and vanilloid receptor1.

In the TPV1 lineage, mice-lacking somatosensory neurons are totally insensitive to any quality or modality of thermal stimuli, including both hot and cold temperatures. TRPV1 neurons are molecularly heterogenous, but in most cold-sensitive neurons labelled with the menthol receptor TPM8 and all presumptive mechanosensory neurons that express the mas-related G protein-coupled receptor D, channel expression is absent. For the majority of somatosensory neurons, including those expressing Mrgprd and TRPM, TPV1 is a broad development marker (McKemy, 2011). The channel opening events are clearly made longer and occur more often by extracellular magnesium(which consists of a potentiating effect on gating. Magnesium dose-dependent potential-attaches TRPV1 through a gating effect but inhibits conductance at the same time. A previous research, in which magnesium potentiated human TRPV1 current elicited by capsaicin in, showed the dual effect of magnesium on gating and permeation (Cao *et al*., 2014).

Structure and molecular pharmacology of TRPV1

The first member of the subfamily TRPV that was discovered and cloned is TRPV1.It has a tetrameric structure consisting of six regions of the transmembrane and a hydrophobic group between the fifth and sixth regions of the transmembrane. Within the cell membrane, both the N-terminus and the C-terminus are located, controlling the protein's functional activity. TRPV1's overall structure was split into upper and lower sections, corresponding to the channel transmembrane and intracellular regions (Du *et al*., 2019).

The TRPV1 transmembrane core region, containing six transmembrane helices per subunit has the same topology and many structural characteristics as potassium voltage-gated channels (Yang & Zheng, 2017). Modulation of the activity of TRPV1 is under the control of many intracellular signals that act on the N-terminal and C-terminal portions of the monomers including phosphorylation (Liddle, 2012). At different temperatures, temperature-sensing ion channels are thought to follow distinct conformations, powered by a substantial difference in free energy between the closed and open states .In other protein regions and channel forms, temperature-driven structural changes have also been proposed (Yang & Zheng, 2017).The amino acids required by different mediators for TRPV1 activation are beginning to be appreciated. Acidic residues situated in extracellular loops near the pore involve the effects of low PH. Low PH seems to have several effects on TRPV1: It increases open chance, partly by stabilising the channel's open conformation and may increase the apparent affinity of capsaicin in. Vanilloid sensitivity between transmembrane domains 2 and 4 of TRPV1 has been traced to many amino acids. Y511 and

S512, two amino acids located in the loop between transmembrane domains 2 and 3, may play a key role in mediating the effects of capsaicin on the activity of TRPV1 (Cortright & Szallasi, 2004). The ankyrin-like repeat domain is connected to the first segment of the transmembrane by a segment of 77 amino acids thought to be heat sensor. The anti-parallel beta-hairpin that points to the ankyrin-like repeat domain of a neighbouring subunit is a visible structural feature within this section(He *et al*., 2017).

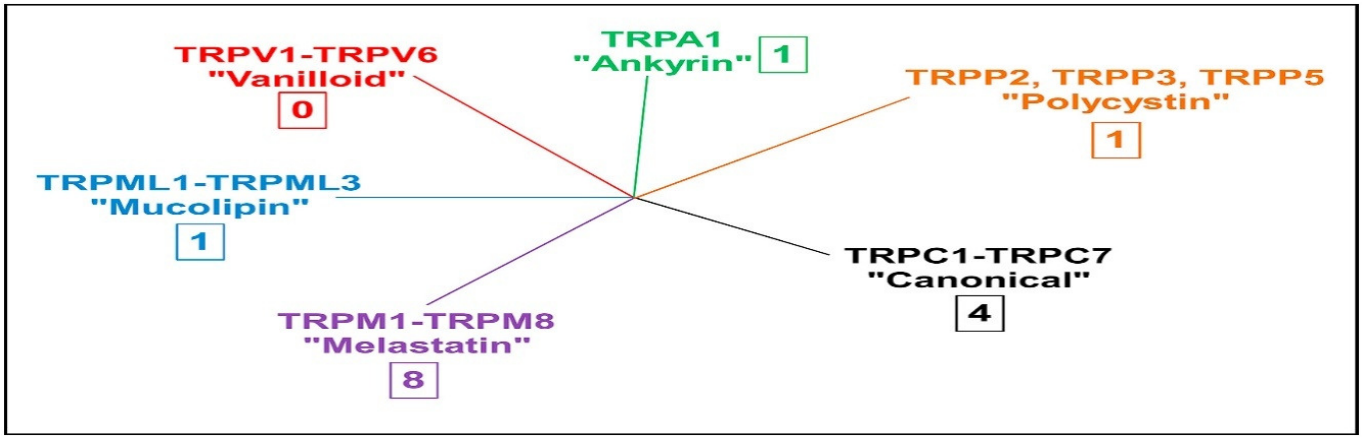

Fig. 1 : Families of TRP channels(Bais & Greenberg, 2018)

Table 1 : Pros and cons TRPV1 antagonists and agonists therapeutic Approaches:(Huang *et al*., 2008)

Therapy	PROS	CONS
TRPV1 antagonist	Avoid pain associated with agonist treatment Rapid action onset (no desenitisation required for effect) Developable orally-active/systemic drugs (ease of use)	Reduced efficacy can be given cf. Defunctionalisation of the agonist with certain indications Not thoroughly researched side effects.
TRPV1 Agonist	Large mechanistic effect of broad mechanistic effect due to sensory neurons 'defunctionalisation well characterized capsaicin and analogues. Long term consequences	Side effects of orally active/systemic treatments tolerability-pain requires concomitant care with local anaesthetic (LA) Delayed onset of active activity.

TRPV1 Expression

- **Neuronal cells:** small to medium diameter primary afferent fibres
- ✓ Sensory neurons**:** myelinated fibres, unmyelinated C fibre. C-fibre neurons are usually polymodal and overlapping populations are triggered by chemical, heat, cold, or mechanical stimulation, possibly reflecting co-expression of transducers responsive to these various stimuli (Brenneis *et al*., 2013).
- ✓ Dorsal root ganglia.
- ✓ Trigeminal neurons
- **Non-Neuronalcells:** keratinocytes, bladder urothelium, smooth muscles, liver polymorphonuclear granulocytes, pancreatic B cells, endothelial cells, lymphocytes, macrophages
- **Brain:** Dopaminergic neurons of substantia nigra, hippocampal pyramidal neurons, hypothalamus (Du *et al*., 2019).

Mechanism involved in activation of TRPV1 channel by capsaicin:

The target of capsaicin (CAPS), the active component of chilli peppers, is considered to be TRPV1 and can also be referred to as the capsaicin receptor. Resiniferatoxin, a phorbol ester isolated from the Moroccan cactus irritant lattices, has a much greater affinity for TRPV1 than for CAPS. Both compounds activate TRPV1, rendering the channel more permeable to cations, leading gradually to an analgesic effect due to desensitisation of the channel (Elokely *et al*., 2016).

Exquisite affinity sensitivity and capsaicin selectivity are shown in TRPV1. Cysteine accessibility measurements indicated that lower portion of S6 moves to open the activation gate with respect to capsaicin induced activation. The capsaicin molecule uses "tail-up, Head-down "configurations. The aliphatic tail interacts with the channel via non-specific vanillyl head, amide neck and the channel give the specificity for ligand binding. Tail-up, head-down binding and pull and contact gating should usually be applicable to capsaicin TRPV1 activation (Long *et al*., 2019). Severe amino acid residues have been identified by mutational studies, which play an important role in binding to vanilloid such as capsaicin and RTX. Three amino acids (L518, F591 and L670) have been recently identified as involved in ligand binding and proton sensitivity modulation (Ohbuchi *et al*., 2016). In certain channels, but not others, activation of protein kinase C (PKC) promotes channel opening, consistent with some channels that are inaccessible to kinase. Following PKC activation, the changes in open and closed state time constants are equal to an increased affinity of capsaicin binding. Number of steps involved in channel activation and which of these steps can be modulated by phosphorylation to improve channel activation (Studer & McNaughton, 2010).

Physiological and pathological functions:

Inflammation and immunity, the cardiovascular system and diseases such as obesity have been implicated in the physiological or pathological effects of non-neuronal TRPV1. Meanwhile, among other things, neuronal TPV1 in the brain may have roles in neurogenesis and thermoregulation (Fernandes *et al*., 2012). TRPV1 can be directly activated by ethanol and a variety of endogenous lipids such as anandamide can directly activate TRPV1 (Vay *et al*., 2012). TRPV1 channels contribute to the regulation of intracellular calcium, which in cases of gene transcription dysregulation and calcium dependent pro-proliferative or anti-apoptotic mechanism may promote cancer hallmarks (Weber *et al*., 2016).

Digestive diseases: TRPV1-like immunoreactivity has been reported in the gastrointestinal tract on nerves inside myenteric ganglia and interganglionic fibre tracts (Geppetti & Trevisani, 2004). The most common form of peptic ulcer is the gastric ulcer, which specifically refers to tissue damage caused by gastric digestive juice outside the mucosal muscle layer. The injection of low dose of capsaicin could suppress the development of ulcers (Du *et al*., 2019). The TRP channels survey the gut environment for a wide range of chemicals and toxins that are either contained in the food and GI tissue, components of the digestive juice, produced by the GI microbiome. TRP channels in the alimentary canal are essential for controlling the membrane potential and excitability of epithelial cells, muscle cells and interstitial cells, playing a role in the absorption of calcium and magnesium, regulating blood flow, pacemaker function, motor activity and homeostasis of the mucosa and influencing the development of GI cancer.

Cardiovascular diseases: Cardiovascular disease, encompassing a number of cardiac and vascular disorders, is leading cause of morbidity and mortality worldwide. Transient receptor potentially vanilloid channels, specially type TRPV1 and Type 2 TRPV2, are relatively newly identified channels located in and around the cardiovascular system in the body. It has been found that the TRPV1 channel is an important player in the diagnosis of chest pain after myocardial injury. TRPV1 channel is localized in the sensory nerves surround cardiovascular structures, near to the heart's epicardial surface and in vascular endothelial cells that line the cardiovascular system arteries (Robbins *et al*., 2013). Deletion of TRPV1 is associated with proinflammatory effects in cardiovascular changes, such as those seen in sepsis, ischemia of the myocardium and hypertension caused by DOCA-salt. TRPV1 can act as a molecular integrator and can play a key role in the development of diseases (Marshall *et al*., 2012). Hypertension is a complex disease that can lead to changes in the function and structure of the heart and cardiovascular system caused by genetic and environmental interactions (Du *et al*., 2019). (Pulmonary arterial hypertension is a pulmonary hypertension subtype with end expiratory pulmonary artery wedge pressure requirements of less than or 15mmhg and pulmonary vascular resistance of more than 3 units of wood. In order to research the role of TRPV1 in the pathogenesis of pulmonary arterial hypertension, TRPV1 is a nonselective cation channel that allows calcium influx, so it is important to explore the calcium signalling pathway (Zhang *et al*., 2019). TRPV1 channel is heavily involved in sensing blood pressure fluctuations. When TRPV1 is triggered in the cardiovascular system-controlled nerve fibres, including the heart and systemic blood vessels, it facilitated the release of SP and CGRP neuropeptides, which are involved in controlling peripheral vasoconstriction and diuresis lowering blood volume to lower blood pressure (QIAN DU). A temporary increase in cochlear blood flow has also been shown to produce capsaicin, possibly by activating TRPV1 containing neurons innervating the spiral changed artery and arterioles and stria vascularis. TRPV1 functions as an integrator of "noxious" stimuli for the activation of the cochlear inflammatory cascade. This process involved coupling TRPV1 to NOX3 and the transcription 1 signal transducer and activator. For the treatment of conditions ranging from chronic pain to hearing loss, medications that could modulate TRPV1channel activity could be useful (Brito *et al*., 2014).

Respiratory diseases: respiratory diseases affect the quality of life of people worldwide. TRPV1 is widely distributed and functionally established as a nociceptor in the sensory nerves fibres of the respiratory system, especially in the cells with C type fibres. TRPV1 can be activated in the respiratory system in a number of endogenous and exogenous ligands including capsaicin, resiniferation and low PH. In order to promote airway inflammation, TRPV1 activation induces the release of proinflammatory cytokines from bronchial epithelial cells, including tumour necrosis factor alpha, prostaglandins and interleukins (Du *et al*., 2019). The afferent behaviour resulting from ends of C-fibre plays an important role in regulating respiratory functions both under normal and under pathophysiological conditions. Capsaicin, a pungent ingredient of chili peppers, is known to activate airway C-fibres and this activation has long been associated with the initiation of several central reflexes, including increases in respiratory rate, parasympathetic bronchoconstriction, mucus hypersecretion, vasodilation as well as urge to cough sensations and sensations of dyspnoea. TRPV1 is located primarily in afferent sensory neurons in the respiratory system. TRPV1, along with tachykinin has been hypothesised to be responsible for releasing neuropeptides from the sensory terminals, thus initiating local neurogenic inflammation (Takemura *et al*., 2010).Airborne particulate matter (PM) and mortality also associated with respiratory and cardiovascular disorder related mortality. Exposure to particulate matter can worsen pre-existing respiratory diseases and also enhance the development of new diseases. A very large variety of solid or liquid particles consists of PM various sizes that are small enough to stay suspended in the atmosphere for long periods. Due to their capacity to produce reactive oxygen species (ROS), both organic and heavy metal PM components have been reported to induce proinflammatory effects and oxidative stress (Agopyan *et al*., 2020).

Properties of TRPV1 in Immune Regulation:

The plasma membrane of resting CD4+ T cells is primarily expressed by TRPV1 (Yang *et al*., 2015) In TRPV1 CD4 +Tcells, the calcium influx caused by anti-CD3 antibody crosslinking was significantly reduced. (Wanner *et al*., 2012). In Tells, TRPV1-specific agonists, namely resiniferatoxin can activate calcium influx. The role of TRPV1 channel in activation of T cells either by ConA or by stimulation of TCR (Majhi *et al*., 2015). TRPV1 was found to be functionally expressed in CD4+ cells. Since CD4+ T cells play a key role in the adaptive immune response. TRPV1-mediated the TCR signalling in CD4+T cells and

stimulated CD4+ T cells derived from TRPV1 significantly secreted by mice higher cytokine levels (Samivel *et al*., 2016).

TRP channels are members of superfamily of tetrameric cation channels for which the composition of the subunit is a significant determinant of the biophysical and regulatory properties of each type of channel. whether thermosensitive TRPV channels are merged into heteromeric channels has major consequences for thermosensing coding and control. These heteromeric channels have unique conductance and gating properties, which can lead to a greater variety of thermosensitive channels functioning (Yang *et al*., 2015).

Role of trpv1 in the process of inflammation:

Inflammation is a process characterised by pain, swelling, increased temperature and redness that can be induced by pathogen infection or tissue damage. The main role of the inflammation is to stimulate the cells to fight against pathogens and regenerate destroyed tissue. It is tightly correlated with the action of immune cells and secretion of pro-inflammatory factors (cytokinin, chemokines) The absence or blocking of the possible vanilloid subtype 1 (TRPV1) Affects the extent of inflammation and fibrosis during wound tissue healing using the corneal alkali burn model in mice. Inflammatory cell invasion and myofibroblast generation were inhibited by TRPV1 loss in combination with decreased expression of pro-inflammatory and profibrogenic components (Sumioka *et al*., 2014). serious and recurrent corneal inflammation and fibrosis were suppressed by the loss of TRPV1 expressed or blockage of its activation, resulting in a marked improvement in the restoration of tissue transparency (Sumioka *et al*., 2014).

TRPV1 as a pain and heat sensor expressed at high level in C-fibres associated with neurogenic pain, was primarily associated with neurogenic inflammation (Elizabeth S. Fernandes *et al*., 2012)TRPV1 was related to the inflammation process basis of the studies that showed:

- Over expression of V1 in inflamed tissues
- Correlation between TRPV1 activation and expression of proinflammatory cytokines (Bujak *et al*., 2019).

It is commonly recognized that TRPV1 is involved in inflammation. The pharmacological blockade of TRPV1 decreased the level of proinflammatory cytokines in chronic asthma and mouse models injected with LPS

TRPV1 and skin

The skin is the largest sensory organ in our body and by detecting numerous disruptions occurring in the boron of the two environments, including thermal disturbances and activating defensive response, it further contributes to homoeostasis. Skin nerves sense ambient temperature and that the skin's environmental thermal signals act as feedforward signals in body temperature control (Romanovsky, 2014). TRPV1-immunoreactive fibres were primarily present in normal skin in the sub-epidermis (Gopinath *et al*., 2005) The release of Keratinocytes of trophic factors such as nerve growth factor (NGF) and artemin can chronically modulate neuronal structure and skin function. The transient receptor potential vanilloid (TRPV) family of temperature sensitive ion channels in keratinocytes has fuelled the notion that keratinocytes are involved in acute thermosensory transduction(Huang *et al*., 2008). Beyond Nociception, the role of TRPV1 in human skin indicates that activation of TRPV1 decreases the proliferation of keratinocytes and delays the recovery of the epidermal barrier(Caterina, 2014). Activation of TRPV1 results in local cutaneous release of neuropeptides such as substance P, (SP) which subsequently activates various types of skin cells, such as keratinocytes, mast cells, antigen-presenting cells, and T cells, which are located close to the sensory nerve endings. SP triggers the release of proinflammatory cytokines through binding to its receptor, resulting in the recruitment to the skin of additional immune cell subsets (Misery *et al*., 2016). TRPV1 is expressed at the highest level in the subpopulation of peptidergic sensory neurons involved in the perception of pain. The first known molecular thermoreceptor was TRPV1, as it can be activated by painfully hot temperature in the absence of chemical ligands. This polymodal chemo-thermo sensitivity accounts for the perception of "heat" experienced during consumption of chili peppers and has led TRPV1 to receive substantial attention as a candidate target got pain control (Caterina & Pang, 2016).

TRPV1 In Pain, itch and Neurogenic Inflammation:

Cutaneous neurogenic inflammation (CNI) is inflammation caused by the excessive release into skin of neuropeptides such as calcitonin-related peptides and tachykinins from local sensory nerve endings. TRPV1 act as nociceptive sensors and facilitate the inflammatory process. Released endogenous mediators' eicosanoids, acidosis, ATP, histamine which further sensitive or activate TRPV1 on skin nerve terminals, contribute to CNI self-maintenance during CNI(Gouin *et al*., 2017). TRPV1 is an important target for the Management of chronic pain. (Bode *et al*., 2009) The foremost application of TRPV1 antagonist is in the treatment of pain. In TRP (TRPV1)-null mice and inhibited by iodoresiniferatoxin, a potent TRPV1 antagonist, acute pain-related behaviour-revoked by elevated ionic strength is abolished. The effects of cation and the physiological concentrations of cations lead to the activation of TRPV1 by bradykinin and heat sensitization of the receptor. Cationic intensity modulation of TRPV1 can contribute to the signalling of inflammatory pain (Ahern *et al*., 2005). Subtype 1 TRPV1 antagonist TRPV1 antagonist also show efficacy in post-operative pain, cancer pain and model of osteoarthritis (Szallasi & Gunthorpe, 2008). TRPV1 antagonist administration to mice, rats and humans, has confirmed roles the function of this channel in pain sensation. Beyond the perception of pain, TRPV1 has been shown to participate in other neuronal functions relevant to the skin for example, TRPV1 null mice exhibit reduced itch related scratched behaviour in response to interleukin or histamine (Caterina & Pang, 2016). In several regions known for their function in pain delivery or regulation, TRPV1 receptors have been identified in the brain. Antinociceptive effects are produced by microinjection of capsaicin into periaqueductal grey, suggesting a functional role of CNS TRPV1 (Cui *et al*., 2006).

The TRPV1 triggered by capsaicin goes into a long refractory state and thus a previously excited neuron is immune to multiple stimuli ranging from mechanical pressure to endo/exogenous pain ad proinflammatory agents (Sharma *et al*., 2013). As used, itching can be caused by a range of chemical stimuli when applied to the skin, which is innervated by a diverse array of primary afferents, including

a heterogenous subset of unmyelinated C-fibres afferents. Selective deletion from primary afferents of a TRPV1 population consists of itch fibres that react to various types of pruritogens (Kim *et al*., 2011). For several years, histamine has been considered a key itch inducing substance. Antihistamines are widely used to treat pruritus, blocking histamine receptors, but occasionally they are unsuccessful. To excite these sensory neurons, histamine requires the activation of TRPV1. In the subset of sensory neurons, TRPV1 and histamine receptors are expressed and primary afferent C fibres that react to histamine are also susceptible to capsaicide. In addition, the application of cutaneous capsaicin also evokes itching and painful sensation (Shim *et al*., 2007).

Histamine is known to produce a TRPV1-dependent form of itch, indicating a role for Part in this process .Histamine has also been shown to stimulate DRG neurons directly and in the presence of a TRPV1 antagonist, this response is decreased (Patel *et al*., 2011). Subset VGLUT2 is an also major player in the thermal nociception of TRPV1 and also helps to regulate a natural itch reaction. Vesicular glutamate transporter (VGLIT) 2 deletion in a subpopulation of neurons slightly overlapping with primary afferents of the vanilloid receptor (TRPV1) resulted in a drastic increase in itching activity followed by a decreased response to thermal pain (Lagerström *et al*., 2010).

TRPV1 And Cancer:

In normal cells such as mammalian neuronal cells and cardiomyocytes well as several forms of tumours including bladder cancer cells, breast cancer cells, TRPV1 has been shown to be highly over expressed. The development of photothermal semiconducting nano agonists that for precise cancer treatment, target the TRPV1 protein ion channel. Such a semiconducting photothermal nano agonist uses semiconducting polymer nanoparticles to deliver the TRPV1 agonist to the tumour site as a temperature-responsive nanocarrier to ensure a high local concentration of the TRPV1agonist at the tumour site with a relatively low systemic dosage (Zhen *et al*., 2018). Cancer pain is a big clinical concern since in 20-25 percent of all cancer patients it is the first symptom of the disease and 90 percent of advanced or terminal cancer patients have to live with persistent pain syndromes due to failed treatment and tumour progression.

A significant percentage of sensory neurons that innervate the tumour-bearing bone express TRPV1 and that TRPV1 expression is maintained even when the invading tumour cells injure the distal processes of these sensory fibres (Yang *et al*., 2015). Within a separate subpopulation of dorsal root ganglion neurons in a bone cancer state, TRPV1 expression was increased and that pharmacological block of TRPV1 in a murine model of bone cancer pain reduced pain-related behaviours. Compared with the effect of morphine alone, the combination of morphine and TRPV1 antagonists greatly reduces bone cancer pain (Niiyama *et al*., 2009). Elevated TRPV1 expression occurs in cancer cells of the colon, pancreas and prostate (Sun *et al*., 2014). Capsaicin has been also shown to have either tumour-promoting or suppressing effects, many of which are mediated by TRPV1 channel (Caprodossi *et al*., 2011). TRPV1 activation in anti-cancer therapy via harnessing the calcium signalling.

Activation of TRPV1 by capsaicin, was shown to significantly reduce proliferation and induce apoptosis triple-negative breast cancer cell line. The functional expression in different cell types of TRPV1 Splice variants (Bujak *et al*., 2019). Epidemiological studies showed that capsaicin has a protective effect against gastric carcinoma. TRPV1 agonist have been in clinical use for decades and no increase in the incidence of cancer in patients with chronic topical capsaicin in has been reported (Szallasi & Gunthorpe, 2008).

The role of TRPV1 is also well known in the function of the bladder and basic scientific evidence supports the function of TRPV1 in regulating the frequency of bladder reflex contractions, including chronically inflamed urinary bladders of rats. In the suburothelium, TRPV1 channels are necessary for normal excitability of low-threshold bladder fibres (Mistretta *et al*., 2014). In paclitaxel cancer chemotherapy, peripheral neuropathy is dose-limiting and can result in both acute pain during therapy and chronic persistent pain in cancer survivors. By sensitising transient receptor potential vanilloid subtype 1 through Toll-like receptor 4 signalling, paclitaxel produces these adverse effects at least partially. Toll-like receptors play major role in acute and chronic itch and pain (Li *et al*., 2015). To research the downstream mechanism of TRPV1 , plasmids from AMPK and CaMKK2 were used (Chen *et al*., 2019).

TRPV1 Skin Appendages:

The skin forms the interface between the inner components of the external environment and the body. In the dermis and epidermis, sensory nerve endings are formed as skin detectors of thermal, chemical and mechanical stimuli (Huang *et al*., 2008). TRPV1 is not only detected in epidermis, dermal blood vessels, mature human keratinocytes, mast cells, appendage epithelial structures, human cultured fibroblasts, human hair follicles and not just in neuronal tissues.

The Epidermal growth factor receptor is a widely expressed tyrosine kinase receptor that plays an important role in regulating epidermal and appendage production In human epithelial cancers, including lung, colon, ovary, bladder, head and neck, EGFR is over expressed and is explored as a possible target for anticancer drugs.TRPV1is a tumour-suppressing membrane receptor associated with the down-regulation of another membrane receptor, EGFR which is essential in the development of skin cancer (Bode *et al*., 2009).

TRPV1-like immunoreactivity has observed in human hair follicles in various epithelial sub compartments, including the outer root sheath and hair matrix. TRPV1 activation suppressed epithelial proliferation and hair shaft elongation in the organ cultures of these hair follicles and encouraged hair follicle regression. In the epithelial compartment of mouse hair follicles, TRPV1-like immunoreactivity was also documented and hair cycle analysis in TRPV1 knockout mice revealed a delayed catagen process(Caterina, 2014).

TRPV1 And Gastrointestinal Diseases:

TRPV1 is typically expressed by spinal and vagal afferent neurons that internalise the gastrointestinal tract where upregulation can lead to the pathophysiology of conditions such as visceral pain, faecal urgency/irritable bowel syndrome (IBS), inflammatory bowel disease and

pancreatitis (Szallasi & Gunthorpe, 2008). Gastric ulcers are the most common form of peptic ulcer, which primarily refers to tissue damage outside the mucosal layer caused by gastric digestive juice. The relaxing effect of capsaicin on the gastrointestinal tract has been considered. However, it has been stated that there is a protective effect on the gastric mucosa by consuming average quantities of capsaicin (Du *et al*., 2019) .

Traditionally, Spicy or hot foods are known as dietary variables involved in peptic ulcer causation. Capsaicin simulates the capsaicin TRPV1 receptor expressed by a primarily afferent nociceptive neuron subgroup. It is gated by low ph., noxious heat and various pain-producing endogenous and exogenous chemicals besides capsaicin and some vanilloids. Therefore, these sensory nerve endings equipped with these ion channels are vulnerable to gastric mucosa stimulation (Mózsik *et al*., 2005). TRPV1-like immunoreactivity has been reported in the gastrointestinal tract on nerves inside myenteric ganglia and interganglionic fibre tracts.

There were TRPV1-immunoreactive nerve fibres associated with them in blood vessels inside the gastrointestinal wall. Within the mucosa, TRPV1-like nerves and other immunopositive cells were also observed. Following stimulation of TRPV1 by each individual stimulus (acidic media, alcohol, high temperature) the sensation of burning pain may be activated but all these stimuli which synergize and burning pain may be exaggerated in a proinflammatory environment where TRPV1 function has been upregulated (Geppetti & Trevisani, 2004).

TRPV1 In Cough:

Cough is one of the most common symptoms of multiple disease that are characterised by inflammation of the airways, such as asthma, chronic bronchitis and chronic obstructive pulmonary disease. Citric acid, capsaicin and resiniferatoxin agents which are commonly used in provocative cough tests in laboratory animals and humans have been shown to act as agonists of the of the TRPV1. Protease-activated receptor-2(PAR2) is part of a family of four receptors coupled with G-protein, which are uniquely activated by tethered ligands. TRPV1-dependent cough in guinea pigs and whether the PAR2-induced cough modulation involves protein kinase (Gatti *et al*., 2020) .Acute cough can be an annoyance, but it is rarely a major cause of concern, whereas chronic cough can ruin the quality of life and cause severe patient and job problems.

Cough as consisting of a three-or four-phase action: 1. the inspiratory period, consisting of a deep inspiration 2.the compressive phase, with the closing of the larynx and a forced expiratory effort.3. The expulsive phase, with the typical first cough tone, when the larynx opens and rapid expiration occurs and 4. The restorative phase, when a deep final breath is taken. Cough may also trigger other airway and lung sensors, although they may not trigger it(Chung, n.d.). Asthma, eosinophilic bronchitis, upper airway cough syndrome, are among the most common aetiologies of chronic cough, available therapies often provide adequate relief in patients with these aetiologies.

Most commonly, capsaicin, a selective TRPV1 agonist, is used to evaluate sensitivity to cough relaxes. There is an increased sensitivity to inhaled capsaicin in patients with chronic cough, which improves after successful treatment (Long *et al*., 2019). Activation of TRPV1 in the airway by the inhaled TRPV1 agonist is significantly more effective than activation of TRPA1 in causing cough (Birrell *et al*., 2014). Cough, like asthma, bronchitis, chronic obstructive pulmonary disease (COPD) and the common cold is arguably the most common symptom associated with pulmonary diseases. chronic cough is a symptomatic expression of hyperresponsiveness to the airway.

Drug target for chronic cough are receptors present on airway sensory nerve-endings and in cell bodies of C-fibres. In the elicitation of cough reflexes, airway sensory nerves that express TRPV1 receptors are involved (Adcock, 2009). In Response to cough-provoking stimuli, including fire, acid and some arachidonic acid derivatives, this channel has gained prominence as a “cough-mediator receptor” because it activates afferent nerve activity. In chronic coughs, TRPV1 expression is increased and upregulated in response to inflammation. There has long been a recognition of the effect of sex hormones on ion channels, explaining certain pathogenic variations between men and women.

In response to uterine cervical distension, TRPV1 becomes essential only in activating afferent nerve fibres after oestrogen replacement therapy. The effect of oestrogen on TRPV1 predisposes the female sex to cough hypersensitivity syndrome (CHS), explaining the higher prevalence of CHS among females. This collaboration will reinforce the hypothesis that TRPV1 is important in cough hypersensitivity syndrome (Patberg, 2011).

TRPV1 And Pancreatitis:

ancreas is an organ whose functions are both exocrine and endocrine. For maintaining the steady state of the pancreas and exercising its normal physiological role, the normal synthesis, storage and secretion of the digestive enzymes from the pancreatic exocrine glands is important. Sympathetic, parasympathetic neurons and sensory nerve fibres dominate the pancreas, which modulate the exocrine and endocrine functions of the pancreas. TRPV1 involved in neurogenic inflammation during acute pancreatitis. Treatment with TRPV1 antagonist substantially decreased pancreatitis severity (Qian Du). The magnitude of caerulein-induced pancreatitis was decreased by antagonist such as capsazepine or by desensitisation of pancreatic primary sensory neurons with RTX. TRPV1 mediates pain in acute pancreatitis (Liddle, 2012) .

Pancreatic sensory (afferent) nerve endings are exposed to a rich environment of inflammatory mediators during acute pancreatitis that sensitise them by mechanism that remain to be determined. In the presence of tissue injury or inflammation, primary afferent neurons have effective functions that mediate neurogenic inflammation. The improved activity of TRPV1 on pancreatic afferent terminals contributes to increased release in the pancreas of proinflammatory neuropeptides (Schwartz *et al*., 2011).

Clinical Development of TRPV1 Antagonists:

Table 2: TRPV1 antagonist in the clinic

Also, active	Preclinical	PHASE I	PHASE II
Amore pacific Amphora	Renovis-pfizer	Amgen AMG517	Glenmark GRC 6211
Astellas AstraZeneca	Sanofi-Aventis SAR-115740	Abbot ABT102	GSK SD705498
			Merck-neurogen MK-2295

A relatively large number of TRPV1 antagonist Have already been tested in humans as of today. Patients with a variety of conditions and symptoms, often involving pain and inflammation (e.g. dental or neuropathic pain, arthritis or dermatitis) were studied in addition to healthy adult volunteers (Wanner *et al*., 2012). Up to six orally active TRPV1 antagonist molecule are put in a clinical development at this time with available public knowledge gathered from patent, literature and company press release. First, SB-705498 has successfully completed phase 1 studies in healthy volunteers, has been tested for migraine and is now being studied in further clinical trials for postoperative dental pain and rectal (Cortright & Szallasi, 2004).

Effect of TRPV1 Antagonist in human clinical trials:

TRPV1 antagonist in humans had an adverse effect on Tb. AMG 517caused pronounced hyperthermia with deep Tb exceeding 40 degree Celsius in one of the first human trials resulting in the premature termination of the experiment. There was no thermal effect in humans with another TRPV1 antagonist, SB-705498, even at doses as high as 600mg p.o. while the NEO6860 mode-selective antagonist seemed to cause a slight decrease in deep Tb (0.2-degree Celsius) TRPV1 antagonist often affect the TRPV1 channel in a species-specific manner and thus have different activation-mode pharmacological profiles in different species against the TRPV1 channel (Garami *et al*., 2020). AMG 517 prevents thermal hyperalgesia caused by inflammation and also cause hyperthermia in multiple species. TRPV1 antagonist block hypothermia caused by capsaicin and cause hyperthermia on their own. Repeated administration of AMG 517 attenuates hyperthermia (Gavva, 2009). TRPV1 antagonists decreases heat sensitivity and increase core body temperature(hyperthermia), whereas burning sensation and acute drop in core body temperature (hypothermia) are triggered by administration of capsaicin, a chemical rich in chilli peppers that triggers spiciness by activating TRPV1 (Luo *et al*., 2019).

Desensitization of Receptor TRPV1 is Decreased by the cyclic AMP-dependent protein Kinase pathway

The capsaicin receptor TRPV1 is one target of the CAMP/PKA signal pathway to sensitize primary sensory neurons. TRPV1 is a non-selective cation channel primarily expressed by primary sensory nociceptive neurons and involved in the detection of noxious stimuli. Prolonged or repetitive TRPV1 activation causes desensitization and receptor insensitivity to subsequent stimuli. PKA decrease the hierologically expressed desensitisation of capsaicin and proton activated TRPV1 currents in Chinese hamster ovary-K1 cells and directly phosphorylates TRPV1 (Mohapatra & Nau, 2003).With needles that are dry heated to 44 degree Celsius, dry needling therapy with heat conduction could affect the abundance of TRPV1, protein kinase C and interleukin(IL)-6 in MRna in rats, which could however be abrogated by a TRPV1 antagonist (G. Wang *et al*., 2019).

Effect of Ageing on the TRPV1 Receptor in systemic inflammation from anti-inflammatory to Pro-inflammatory:

The leading cause of death in hospitalised patients is systemic inflammatory response syndrome (SIRS). SIRS is considered an elderly disease: its prevalence and mortality in the older population are significantly higher.Activation of TRPV1 on sensory nerves strongly inhibits development of TNF alpha induced by LPS. TRPV1 plays an anti-inflammatory function in LPS-induced SIRS by limiting the development of TNF alpha, likely through sensory nerves among other mechanism (Wanner *et al*., 2012).

Plasticity of TRPV1 in airway diseases:

Central and local reflex events such as bronchoconstriction, airway plasma leakage, mucus secretion and cough are controlled by sensory nerves in the airways. In the airways, via an afferent central reflex pathway, activation of rapidly adapting stretch receptors and C-fibres triggers cough, bronchoconstriction and mucus secretion.

On the dorsal root ganglion membranes, unique binding sites for resiniferatoxin have been demonstrated and secondly caps azepine has been found to inhibit various capsaicin-evoked neuronal responses including those in the airways (Birrell *et al*., 2014). Initially, TRPV1 channels were thought to be restricted to nociceptive neurons and were shown to express strongly in dorsal root, trigeminal and vagal ganglia. TRPV1-positive nerve fibres internalise the entire respiratory tract, including upper airway nose, larynx and trachea, lung parenchyma, alveoli, smooth muscle and blood vessels. In patients with emphysema, TRPV1 mRNA expression in lung tissue is increased as compared to stable non-smokers (Grace *et al*., 2014). For the treatment of asthma and chronic obstructive pulmonary disease, inhaled muscuranic receptor antagonists are currently used as bronchodilators. In a prospective, randomised double-blind, placebo-controlled clinical trial, tiotropium inhibits capsaicin (TRPV1 Agonist) induced cough in patients with upper respiratory tract infections. Tiotropium is capable of using a variety of approaches, directly modulate airway sensory nerves and thus tussive responses (Birrell *et al*., 2014).

In patients with airway inflammatory disorders such as asthma, bronchitis, viral infection etc airway hypersensitivity characterised by exaggerated sensory (e.g., airway inflammation, dyspnoea, etc) and reflexogenic responses (e.g., cough, bronchoconstriction, etc.) to inhaled irritants and certain endogenously released mediators, is a popular pathophysiological characteristic (He *et al*., 2017). The studies have further also shown that increased TRPV1-mediated responses in some chronic airway diseases are associated with increased TRPV1 channel expression in

bronchopulmonary sensory nerves. During the airway inflammatory reaction, the plasticity of TRPV1 grows through the action of different inflammatory mediators and cytokines (G. Wang *et al*., 2019).

Effects of TRPV1 agonist vs antagonist against nicotine induced depression-like behaviours:

Nicotine (NC) is the tobacco addictive drug that results in increased use by adolescents and has been reported to have various adverse effects for both men and women. The ability to change mood levels (e.g. depression, anxiety etc.) is a trait of NC, as checked before head. A major 'antidepressant' attenuation was triggered by the TRPV1 agonists against the NC-induced depression-like behavioural changes, as well as the IM- induced depression-like behaviours. On its own, the TRPV1 antagonist CZ did not have any major effects against depression-like behavioural modifications triggered by NC and IM. A decreased fear memory indicative of an impairment in stress coping and anxiolytic-like behaviour by promoting protective responses was induced by the blockade of TRPV1 receptors and direct behavioural changes triggered by CZ could be predicted (Hayase, 2011).

TRPV1 in dextran sulfate-induced colitis in mice:

Oral dextran sodium sulphate (DSS) and topical trinitrobenzene sulfonic acid (TNBS)-induced colonic inflammation are the most studied animal models of ulcerative colitis and crohn's disease. Progressive crypt loss in the colonic mucosa, alterations of luminal bacterium species and activation of inflammatory cells are the pathological basis of DSS-induced colitis. Inhibitory action on TNBS (topical trinitrobenzene sulfonic acid) and DSS-evoked colitis in rodents is exerted by various TRPV1 receptor antagonist (Szitter *et al*., 2010).

Epithelial TRPV1 Signalling Accelerates Gingival Epithelial cell proliferation:

By forming a physical barrier defending against exogenous noxious agents, gingival epithelial cells (GECs) lead to homeostasis in periodontal tissues. Additionally, by activating pathogen recognition receptors, including Toll-like and nucleotide-binding oligomerization domain (NOD) like receptors, GECs sense and respond to bacterial stimuli. TRPV1 is expressed by GECs and is involved in the gingival epithelium's cellular functions. Epithelial barrier destruction and the resulting penetration of exogenous substances into the gingiva facilitate periodontal breakdown progression. This pro-proliferative effect was prevented by pre-treatment of epi 4 cells with the TRPV1 antagonist (Takahashi *et al*., 2014).

Effect of Hypoxia on TRPV1:

Hypoxic pulmonary vasoconstriction is caused by acute hypoxia, a particular adaptive physiological response of the pulmonary circulation to ensure effective oxygenation of the blood. In particular, TRPV1 appear to be strong candidates for connecting hypoxia-induced effects with vessel remodelling. Hypoxia-sensitive transcription factors or indirectly via the increase of pulmonary arterial pressure during the establishment of HPV and PH. Indeed, due to the position of PASMC in the arterial wall, SAC is directly transduced by an elevation in intraluminal pressure, which can serve as a signal transducer, thereby providing a feedback mechanism. (Parpaite *et al*., 2016)The capsaicin-induced TRPV1 current was also reduced reversibly by hypoxia (Kim *et al*., 2012). The TRPV1 channels expressed on sensory neurons give rise to cardioprotective effects during ischemic reperfusion injury by inducing the release of neuropeptides. Consistent with TRPV1 activation, challenging of H9C2 cells with hypoxia activated the phosphorylation of TRPV1 (Sun *et al*., 2014).

Effect of TRPV1 deletion in impaired fracture healing:

All the fracture calluses of the wild- type group showed bony connective junctions between the fracture gaps after 4 weeks post-operative and the callus size was smaller, while the TRPV1 knockout fracture callus still had an evident fracture gap and show a large callus. The findings showed that fracture healing was hampered by TRPV1 deletion (He *et al*., 2017).

The TRPV1 channel is also activated by ethanol and this may be essential for some of central and peripheral actions of ethanol. The other effect of TRPV1 deletion in mice also alters the behavioural effects of ethanol (Blednov & Harris, 2009).TRPV1 deletion increased in wistar or Dahl salt-resistant rats fed a high-salt but not a normal salt diet. This indicates that high-salt intake will activate TRPV1 providing a protective effect (Wang *et al*., 2008).

Effect of Parathyroid Hormone-Related peptide:

Parathyroid hormone-related peptide (PTHrP) is highly expressed in breast and prostate cancers with bone metastasis and is essential for the development and proliferation of these tumours in the microenvironment of the bone tumour. PTHrP causes both heat and mechanical hypersensitivity which depends on the vanilloid family, member of the pain-transducing transient receptor potential channel (Shepherd *et al*., 2018). By upregulating the TRPV1 channel function, PTHrP could potentiate sensory neuron excitation, thus providing a mechanism for sensitizing peripheral pain.

Through PKC-dependent enhancement of TRPV1 currents, PTHrP improved sensory neuron excitability. In addition, Src-dependent increase in TRPV1 plasma membrane levels were caused by PTHrP, resulting in an increased proportion of functional TRPV1-expressing Neurons. A crucial role in peripheral nociceptor sensitization (Gatti *et al*., 2020). By PTHrP for increased TRPV1 trafficking (Shepherd *et al*., 2018).

Role of Capsaicin in Metabolic health:

The superfamily of transient receptor potential (TRP), which has been associated with a variety of biological functions (Dias, Vera Junn, Eunsung Mouradian, 2008). TRPV1 receptor also play an important role in the control of homeostasis of glucose, and TRPV1 receptor could contribute to diabetes development and progression, including both type 1 diabetes mellitus and type 2 diabetes mellitus. TRPV1 is generally expressed across the entire body, including sensory nerves fibres that regulate the release of insulin from pancreatic beta cells and in areas of the brain that control liver function. Capsaicin, an exogenous agonist of TRPV1 receptors, has been shown to minimise food consumption and to increase animal and human energy expenditure (Shepherd *et al*., 2018). several significant risk factors including visceral obesity, hypertension, insulin resistance and dyslipidaemia are associated with metabolic syndrome (Krupkova *et al*., 2017).

The activation of brown adipose tissue is another interesting TRPV1-dependent consequence of capsaicin ingestion. In the digestive tract, activation of TRPV1-expressing neurons sends a signal through the vagal nerve to the brain, this in turn evokes an activation of sympathetic neurons selective for brown fat. I. e the heart rate is not affected. The effect of capsaicin ingestion on metabolic rate, respiratory quotient and appetite has been tested in several clinical trials.

Capsaicin can modestly increase energy expenditure, thus increasing fat oxidation and reducing appetite, contributing to weight control effects (McCarty *et al*., 2015).A functional agent that helps to avoid obesity can be known to be dietary capsaicin. However, since the long-term intake of capsaicin may be limited by its pungency, it is not suitable for controlling obesity in humans. Capsaicin, a widely recorded symptom of painful neuropathy, is generally used topically to relieve aches and burning sensation. It is usually used to alleviate the discomfort of peripheral neuropathies such as topical creams and high dose dermal patches (Lee *et al*., 2013). In several metabolitically active tissues, TRPV1 is present, making it a potentially important target for metabolic interventions. The major components of metabolic syndrome are insulin resistance and obesity, which raise the risk of developing cardiovascular disease, type 2 diabetes and non-alcoholic fatty liver disease. Capsaicin works via the vanilloid type-1(TRPV1), with six putative transmembrane domains and a calcium permeable pore region, a transmembrane cation channel that prefers Ca^{2+} over Na^{+}. In various cells and tissues, TRPV1 is expressed throughout the body, including the heart, liver, kidney, pancreas and adipocytes. capsaicin is an important factor in targeting metabolic syndrome because of the presence of TRPV1 in these metabolically active tissues (Panchal *et al*., 2018).

Conclusion

The first member of the subfamily TRPV that was discovered and cloned is TRPV1.It has a tetrameric structure consisting of six regions of the transmembrane and a hydrophobic group between the fifth and sixth regions of the transmembrane. The target of capsaicin (CAPS), the active component of chilli peppers, is considered to be TRPV1 and can also be referred to as the capsaicin receptor. Inflammation and immunity, the cardiovascular system and diseases such as obesity have been implicated in the physiological or pathological effects of non-neuronal TRPV1.The plasma membrane of resting CD4+ T cells is primarily expressed by TRPV1.TRPV1 as a pain and heat sensor expressed at high level in C-fibres associated with neurogenic pain, was primarily associated with neurogenic inflammation. genetic deletion of TRPV1 in the mouse model of LPS-induced renal and hepatic inflammation and allergic contact dermatitis, led to severe inflammation. TRPV1 also play a role in pain, itch, neurogenic inflammation, cancer, skin appendages, pancreatitis, gastrointestinal diseases and other inflammatory diseases. Up to six orally active TRPV1 antagonist molecule are put in a clinical development at this time with available public knowledge gathered from patent, literature and company press release.

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