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Review Article

TARGETING TRPV1 SIGNALING PATHWAY THROUGH NATURAL PRODUCTS IN INFLAMMATORY CANCER

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ABSTRACT

TRPV1 (Transient potential vanilloid 1) receptor or the vanilloid (capsaicin) receptor, is a heat-activated non-selective cationic channel which gets affected by inflammation causing mediators and hence leads to acute and chronic pain. It is present on sensory nerves and need activation by specific stimuli like bacterial endotoxins, osmostic stress, pH, ROS, temperature to cause initiation and modulation in inflammation and pain. Another major implication of TRPV1 is its use in cancer therapy. Being activated by compounds like capsaicin, it shows different mode of action in different models. Anti-nociceptive effect of capsaicin is well known whereas its anticarcinogenic activity involves an increase in intracellular Ca2+ signaling leading to apoptosis of targeted oncogenic cells. Capsaicin is not the only phytoconstituent which activates TRPV1 channel, but a bunch of other compounds like piperine, cannabidiol, eugenol, ginsenosides also show their TRPV1 based activity. This review mainly focused on such natural products which show both anti-inflammatory as well as anti-carcinogenic activity, in order to recommend their use in inflammatory cancer. It also summarises some other compounds as well which show their action on TRPV1 either analgesic or anti-inflammaotry and proposed their study in chemotherapy.

Keywords: TRPV1, Inflammation, Inflammatory cancer, Capsaicin, Ca^{2+} signaling.

1. INTRODUCTION

Currently, the second foremost cause of mortality in the world is cancer after the cardiovascular diseases, as per WHO. Recently, more focus is directed towards various parameters like inflammation which shows a high prevalency in the cancer patients. For this purpose, the immune response has been a part of various studies as it provides a tumor microenvironment formed or shaped in the presence of pro- or anti-inflammatory cytokines and consequently modulate the tumor development. Such data provoked the probe to develop such approaches that can target this TME so that immune system can tackle the tumors on its own. As a result, a keen interest is shown in the agents (or molecules) that can attenuate tumorigenesis, induce apoptosis, modify immune response or affect TME [1].

A well-established knowledge about the implication of ion channels in various physiological processes in both excitatory and non-excitatory pathways is available and its a significant part of this review. These ions channels are well known in maintaining the up- and down-regulation of cell death. Such relationship between ion channels and cell death poses its role in the uncontrolled cell multiplication, oncogenic cell survival and its migration that can cause metastasis [2, 3].

TRPV1 is such an ion channel involved in the afore-mentioned mechanisms. TRPV1 is, actually, a member of TRPV (Vanilloids) which is one of the subfamilies of TRP ion channels family. Other subfamilies include the TRPC (Canonical), TRPML (Mucolipins), TRPP (Polycystins), TRPM (Melastatins) and TRPA1 (Ankyrin). There are cumulatively 28 members from this huge family of non-selective ion-channels. They accept several stimuli like bacterial endotoxins, osmostic stress, ph, ROS and temperature to get activated. Many natural products also show their activity on this receptor such as capsaicin, menthol, piperine, geraniol and many more to be observed further in this paper [4]. The primary association of TRP ion channels are with sensory nerve cells but recently performed studies also found their expression on other type of cells like immune cells such as dendritic cells, T-lymphocytes, or macrophages [5]. From members of vanilloid receptor subfamily, TRPV1 was the first TRP ion channel to be identified and most extensively studied till date. Julius group, in 1997, was the first one to characterize TRPV1 as acapsaicin receptor

which is a pungent compound found in chilli peppers. [6]. Additional studies unveiled that TRPV1 ion channel also gets activated by protons, temperature and bacterial toxins like LPS (lipopolysaccharides) [7, 8]. TRPV1's association with nociception and thermoception was based on the above-mentioned studies only. Instead such factors which just activates this ion channel, there are many factors which affect TRPV1's activation threshold. For instance, divalent ions from extracellular side such as Mg^{2+}, cause activation of TRPV1 at comparatively low temperatures [9].

Capsaicin was first extracted in 1816 and was isolated in pure form in 1876. Then, in 1919, the structure was first determined and in 1930, it was synthesized chemically. Capsicum genus contains capsaicinoids viz. capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin. 90% of them are capsaicin and dihydrocapsaicin however out of that 90% content; 80% is capsaicin. This molecules act on almost all the factors which were being influenced by TRPV1's expression [10]. TRPV1 is also called capsaicin receptor as capsaicin was the first clinically found stimulant of TRPV1 ion channel [6].

2. AIM AND OBJECTIVES OF THE STUDY

This study was aimed for the first time to gather and compile the recent information about the studies pertainning to the use of natural products to treat inflammatory cancer via TRPV1 signaling pathway. The key objectives of the study are as follows:

- To provide an overview of drugs which show their action via TRPV1 channel, especially the natural products.
- To find the use of such natural products in the chemotherapy mainly the inflammatory cancer.

2.1. Methodology

Author tried to gather and record dispersed information from different sources relevant to natural products targeting TRPV1 in this study. A systematic literature search was conducted from various databases like Pub Med, Science Direct and Google Scholar to get knowledge about various agents targeting TRPV1 and their implications on the basis of various keywords such as TRPV1 , TRPV1+Natural, TRPV1+Herbal, TRPV1+ inflammation, TRPV1+Cancer and number of Web hits from different databases was recorded using Boolean information retrieval system utilizing keyword of the bioactive compounds with "AND" followed by "TRPV1".The detailed search strategy is presented in table 1. The last date of search was November 13, 2020.

The number of web hits on Pubmed was found to be 6725 on searching the keyword "TRPV1" while it was 74600 on Google scholar and 11766 on Science direct. While searching the keyword "TRPV1+Natural" there was a drastic decrease in web hits that is 449, 26200, and 2946 on Pubmed, Google Scholar, and Science Direct respectively.

In addition to this, the web hits were 559, 37900 and 3705 on searching the keyword "TRPV1 + Cancer" on Pubmed, Google Scholar, and Science Direct respectively.

Table 1: Table showing the search strategy for literature search on targeting TRPV1 signaling pathway through natural products in inflammatory cancer

S. No.	Search Engine	Search Keywords	Hits
1.	Pubmed	TRPV1	6725
2.	Pubmed	TRPV1 + Natural	449
3.	Pubmed	TRPV1 + Herbal	63
4.	Pubmed	TRPV1 + Inflammation	1332
5.	Pubmed	TRPV1 + Cancer	559
6.	Google Scholar	TRPV1	74600
7.	Google Scholar	TRPV1 + Natural	26200
8.	Google Scholar	TRPV1 + Herbal	7470
9.	Google Scholar	TRPV1 + Inflammation	43100
10.	Google Scholar	TRPV1 + Cancer	27900
11.	Science Direct	TRPV1	11766
12.	Science Direct	TRPV1 + Natural	2946
13.	Science Direct	TRPV1 + Herbal	527
14.	Science Direct	TRPV1 + Inflammation	6069
15.	Science Direct	TRPV1 + Cancer	3705

2.2. Findings of the literature search

This study is based on the significance of natural drugs targeting TRPV1. As a lot of natural products as being used to treat cancer, newer mechanism of actions shows a great potential towards it. The first part of this literature based study focus the significance of TRPV1 which was followed by a review on drugs acting on TRPV1.

3. DISCUSSION

3.1. Family of TRP Channels

TRP channels are one of the main kind of communication system inside mammalian bodies which leads to a number of signaling pathways. In mammals, these TRP channels are formed as 6-TM (six-transmembrane) cation permeable channels which are classified, based on their AA sequence homology, into 6 subfamilies viz. TRPV, TRPA, TRPM, TRPML, TRPC and TRPP. All these subfamilies show specific functional properties, which makes it difficult to define TRP channels in single term [4]. However, they are called as calcium-permeable cation channels with polymodal activation properties. These channels seems to be adapted to show their action in cellular sensation as they integrate many associated stimuli and couple their action to amplify downstream cellular signal via calcium permeation and membrane depolarization. We, in this review, focused on TRPV1 channel which is one of themember of TRPV subfamily of TRP channels [11].

3.2. TRPV1 signaling pathway

The most common implication of activation of TRPV1 receptor is the spiciness produced when we consume chillies. Capsaicin, which is obtained from chillies, was first used to clone TRPV1 receptor [12]. It was a hot topic by then, as expression of TRPV1 in some of the sensory neurons indicates its role in the detection and transmission of painful stimuli for its involvement in thermoception and nociception [13].

It is not only expressed in sensory neurons but also in GIT [14], pancreatic beta cells [15], skin [16], urinary epithelial cells [17], airways [18] and immune cells as well. It functions in the other parts include: urinary bladder functions [17], airway hypersensitivity [18, 19], insulin sensitivity [20], T cells activation [21].

Many studies [1] uncovered the therapeutic potential of TRPV1 in physiological conditions other than pain like inflammation, change in immune response and cancer. Considering anti-inflammatory role of TRPV1 channel, there are ample of promising studies which show that lack of expression of or blocking of TRPV1 modulates inflammatory response in various models [22-24].

Mechanism of action of TRPV1 includes its activation by various stimuli which leads to enhancement of the intracellular calcium signaling and upregulation of apoptosis due to increase in intracellular reactive oxygen species (ROS), and the activation of caspase 3 and caspase 9. Such cytotoxic changes showed a way for TRPV1 agonists to be used in chemotherapy [25].

3.3. TRPV1 and inflammation

First of all, 'what is inflammation?' Inflammation is a process or adaptive response characterized by pain, swelling, redness, and increased temperature that can be triggered by some noxious stimuli or conditions like tissue damage or infection. Role played by inflammation here is the stimulation of various cells to combat against destructive pathogenic organisms and to regenerate the destructed tissue. There is a tight correlation between the immune system and inflammation i.e. immune cells' action and pro-inflammatory markers' secretion e.g. chemokines and cytokines [1, 26]. Recently, inflammation's process is attaining plethora of attention as it is associated with many pathophysiological conditions like neurogenerative,metabolic, autoimmunological diseases but also formation of tumor and progression of cancer [27-30].

TRPV1 is known to be expressed in higher levels in C-fibers which have association with neurogenic pain as well as primarily known neurogenic inflammation [31]. However, its expression was also observed on non-neural cell-types at genetic level i.e. in mRNA and proteins, which leads the current studies related to TRPV1 in inflammatory diseases such as IBD, rheumatoid arthritis orasthma [32-34].

In the process of inflammation, the involvement of TRPV1 is indefinite. The TRPV1 activation was primarily linked with the triggering of inflammatory responses, even though the current studies described its role as anti-inflammatory target. Basic associatiation of TRPV1 with inflammation can be unveiled by: 'its overexpression in inflamed tissues'; 'correlataion between expression of proinflammatoty cytokines and TRPV1 activation'; 'reduction ininflammation by using TRPV1 antagonist'.

Many studies evaluated the TRPV1's role in inflammation process *i.e.* pharmacological or genetic modulation of TRV1 cationic channel can excite the

inflammation symptoms. However, there are plethora of other studies as well which showed the role of TRPV1 in reducing inflammation. Some of these studies are mentioned below in tables.

From the tables 2 and 3, it is clear that TRPV1 have both proinflammatory and anti-inflammatory properties which represents its immune-protective role in the body. In the process of inflammation, TRPV1 is regulated at various levels i.e. from gene expression to post-transcriptional modifications and cellular compartmentalization. The uncertainty about actual role of TRPV1 arises, when the association of other inflammatory mediators and regulatory proteins is considered in the process of inflammation. Its expression and interaction on different cells concludes the final outcome of TRPV1 activation.

Table 2: Pro-inflammatory effects of TRPV1 in the inflammation process through activation by capsaicin or by blocking/genetic deletion

Activator/Blocker	Model	Dose	Time	Outcome	References
AMG-9810	Mice with LPS-induced sepsis	30 mg/kg/ injection	Administrated 30min before LPS injection	Increase cardiac dysfunction Decrease sensitivity to LPS	35
FA	Mice model with FA (Formaldehyde) and PM induced asthma	2.44 ppm	for 3 h/day	Increase neurogenic inflammation Increase substance P, CGRP levels	36
PM		Exposure toPM <2.5μm	8 h per day		
Acidic pH (5.0)	HET-1A (Human esophageal epithelial cells)	---	12-min on seven occasions over 48 h	Increase MCP-1, IL-8, MIP-1α Production	37
TRPV1 genetic deletion	TRPV1 mice with peritoneal sepsisinduced by LPS	---	---	decrease blood pressure Increase hypotension, hypothermia Increase liver edema	38

Table 3: Anti-inflammatory effects of TRPV1 in the inflammation process through activation by capsaicin or by blocking/genetic deletion

Activator/Blocker	Model	Dose	Time	Outcome	References
Capsazepine	-Mice with chronic asthma	50 μg	Injections daily for 3 months	decrease airway inflammation decrease hypersensitiveness decrease levels of cytokines	39
	-LPS-activated-murine-macro-phage-like-cells (J774.1)	10μM	Preincubated with CPZ30min before LPS	decrease proinflammatory cytokines production decrease COX-2 expression	40
	-Mice with LPS-induced lung injury	15 mg/kg	Single dose injection	decrease area of collapsed lung parenchyma decrease respiratory system resistance decrease tissue damping during endotoxemia	41
Capsaicin	Human-umbilical-vein-endothelial-cells (HUVEC)with LPS treatment	3-10μM	6 h	decrease cytokine/ chemokine production decrease adhesion molecule expression	42

	Mice with LPS-induced bone inflammation	30μM	24 h	decrease prostaglandin E production decrease inflammation decrease bone resorption	43
	Rats with induced sepsis	75 mg/kg 50 mg/kg	Injection on day 1 Injection on day 2	decrease rat's mortality	44
PAC-14028	Hairless mice with induced atopic dermatitis	1.0% PAC-14028 cream	Topical application on skin 2 times a day for 11 days	decrease inflammation cream Increase functions of skin barrier decrease IL-13, IgEand IL-4 production	45
AMG9810	LPS-activated murine macro-phage-like cells (J774.1)	10μM	Preincubated 30min before LPS administration	decrease COX-2 expression decrease pro-inflammatory cytokines production	40
TRPV1 genetic deletion	TRPV1-deficient mice with Arthritis	---	---	decrease bone erosion, synovial inflammation, cartilage damage	32

3.4. TRPV1 and cancer

It is extensively known that there is association of inflammation and tumor formation along with the abnormal calcium signaling which promotes the tumor microenvironment as well as proliferation, metastasis, and cancer cell survival. As both processes of calcium signaling and inflammation are linked to TRPV1, thus it gained more attention in the process of cancer progression. Many studies showed the functional expression of TRPV1 in various tumor types which includes human-papillary-thyroid-carcinoma BCPAP cells, glioma, human-breast-cancer cell lines (BT-20 and MCF-7), urothelial cancer cells and prostate cancer cells (LNCaP and PC-3) [46-50]. A study showed the association of TRPV1 expression downregulation and urothelial cancer progression [51]. Other contradicting study explained upregulation of TRPV1 in various native breast cancers in comparison to healthy tissue [47]. Thus, using TRPV1 expression as a prognostic marker is a potential target for various carcinomas.

Other studies which explained the TRPV1 role in mediation of inflammation as well as cancer are (1) development of colon cancer due to existing TRPV1 induced IBD [52, 53], (2) development of colitis associated cancer in TRPV1-deficient mouse in the distal colon [54]. Such dilemma in the activation or deficiency of TRPV1 along with proinflammatory as well as anti-inflammatory activity of TRPV1, made its role unclear in the process of tumorogenesis.

Such implications demonstrated the potential of using TRPV1 activating agents as anti-cancer therapy. The key role played in anticancer therapy is the enhancement of calcium signaling. Various studies [47] showed the reduction the proliferation and induction of apoptosis in aggressive triple-negative-breast-cancer cell line (SUM149PT) by the activation of TRPV1 using a stimulating agent (capsaicin 150 μM, in this study). On the contrary, other studies detected that in spite of presence of expression of TRPV1 protein in the prostate (LNCaP, Du 145, PC-3) and breast carcinoma (BT-474, MDA-MB-231, MCF-7), there was no cytotoxicity on the administration of capsaicin at 50 μM dose [55]. Although, when cDNA coding human TRPV1 was used to transiently transfect such cells, calcium ion accumulation was observed in mitochondria, on administering lower doses of capsaicin 2 μM, which leads to apoptosis. Such unexpected outcomes are related to other factors which are mediated by or mediates TRPV1 signaling pathway. In addition to this, there are studies which show the action of capsaicin in a TRPV1 independent signaling pathway. For example, capsaicin was found to inhibit beta-catenin/TCF-1 signaling in pancreatic-cancer-cells [56]. Also, capsaicin treatment in the osteosarcoma MG63 cells [57] showed an increase in phosphorylaltion of AMPK and p53 independent of TRPV1 signaling. Similarly, administration of capsaicin in TPA-promoted skin carcinogenesis [58] evaluated its co-carcinogenic activity by the activation of EGFR/Akt pathway which was irrespective of its TRPV1 induced calcium signaling.

3.5. Natural products as a possible modulator of TRPV1 pathway

From years, natural products are been used as pain releivers as well as anti-cancer therapeutics, still the

presice action of most of them is still unclear. There are many pathways to be considered when it comes to mechanism of action of such natural agents. One of such pathway is TRPV1 signaling pathway which actually involves the activation of TRPV1 non-selective cation channel by agonists and shows their antinociceptive, anti-inflammaoty as well as anti-carcinogenic action. Observing such pleiotropy, we will study its various roles which finally lead us to its use in inflammatory cancer. Before that, here are the natural agents which modulate TRPV1.

3.5.1. Capsaicin

Capsaicin is derived from red peppers *i.e. Capsicum annuum*. As mentioned above in this paper, the fruits of red peppers contain various capsaicinoids, out of which capsaicin and dihydrocapsaicin (6,7-dihydro derivative of capsaicin) are the main active constituents [59]. Various studies determined the potential of topical application of capsaicin dosage forms to treat dermatitis by desensitizing TRPV1 whereas oral administration is associated with its other uses like anti-cancer properties due to enhanced calcium signaling. Other studies demonstrated its role as a combination therapy with other well-known drugs in order to increase their efficacy.

3.5.2. Piperine

Piperine is a natural based alkaloid from plants of Piperaceae family, such as long pepper (Piper longum) and black pepper (Piper nigrum). In TCM (traditional Chinese medicine), black pepper has been used for treatment of seizure disorders. It has well known activity in promoting digestive processes and also the anti-inflammatory activity. It was first found as TRPV1 agonist when it showed inhibition on binding sites of [3H]-RTX in the dorsal horn of pig spinal cord [60]. Other similar evidence was activation of inward currents by piperine in TG neurons which relates with capsaicin [61]. One recent study detected that the piperine's effect at human TRPV1 expressed in HEK293 is not similar to capsaicin, but its efficacy is more than that of capsaicin for both desensitization as well as activation of TRPV1 [62]. This better efficacy of piperine than capsaicin *i.e.* desensitization to excitation ratio is still unclear. One possible prospect is the structural difference between capsaicin (vanillyl moiety) and piperine (methylendioxy group, a well-known inhibitor of CYP450 metabolism) [63]. On the other hand, in promotion of dephos-phorylated (inactive) state in TRPV1, piperine might be more potent than capsaicin. One way or other, above findings proposed piperine as template structure for designing and synthesizing improved and better agonists of TRPV1.

3.5.3. Eugenol

Eugenol is the major component of clocimum oil or clove obtained from *Ocimumgratissimu*m and *Eugenia carophyllata*. Chemically, it is an allylbenzene compound with an allyl chain-substituted guaiacol moiety. The isolated eugenol was able to activate inward currents in TG neurons and hTRPV1-HEK293 cells. Its action at the TRPV1 receptor was indicated when it prevented capsazepine completely [64]. This study concluded that it shows anti-nociceptive properties comparable to capsaicin.

3.5.4. Resiniferatoxin

Resiniferatoxin is another TRPV1 channel agonist which is obtained from the dried latex of plant *Euphorbia resinifera* [65]. Previous studies explained the use of this extremely irritant diterpene when its crude form (dried latex) was used to mitigate chronic pains or applied on dental cavities to suppress tooth-ache [66]. Sharing a homovanillyl group with capsaicin, these natural compounds are collectively called vanilloids. Significant findings about RTX are its potency for neurogenic inflammation and thermoregulation, which is 3 to 4 times more than that of capsaicin [67].

3.5.5. Ginger

Ginger Products are comprised of compounds which are isolated from *Zingiber officinale*. The main compounds are gingerols and others are: zingerone, shaogol and paradol. Eventhough the alkyl carbon chain length in shaogols and gingerols varies, still an increase in intracellular calcium signaling was noticed in TRPV1-expressing HEK293 cells of rat [68]. Shogaols showed more potency than gingerols in this prospect. A study represented evoking of capsaicin like ion currents and calcium transients in DRG neurons by [6, 8]-gingerols and both effects were sensitive to capsazepine action [69]. [10]-shogaol, which is only non-pungent compound among shogaols and gingerols, also indued nociception in rats via TRPV1 when it was injected subcutaneously to the hind paw. So, both shogaols and gingerols are activators of TRPV1 channel [68].

3.5.6. Evodiamine

Evodiamine is obtained from the extract of fruits of *Evodia rutaecarpa*. Traditionally, in the Japanese and

Chinese medicine, its fruits used to be prescribed for treating cold temperature induced vomiting, headache and thoraco-abdominal pain. In literature, Evodia is referred as an herb of hot nature. Being a genuine agonist of TRPV1 channel, its MOA is supposed to be similar to that of capsaicin. It causes increase in intracellular calcium and in extracellular uptake in TRPV1 expressing CHO cells in rat. Both of these effects were antagonized competitively by capsazepine, a TRPV1 blocker and a capsaicin antagonist [70]. A combination of nociceptive and anti-nociceptive action was observed in an in-vivo administration of evodiamine on sensory neurons which determines that this natural product both desensitizes as activates the TRPV1 channel sensory afferents. Only difference was that the nociceptive action was dose dependent whereas the anti-nociceptive action was observed at higher doses. On the contrary, it doesn't taste hot, which proposes its mechanisms to be other than that of activating TRPV1 channel [71, 72].

3.5.7. Cannabidiol

Cannabidiol is one of the chemicals obtained from a group of chemical secondary metabolic products found in *Cannabis Sativa*, commonly known as cannabis plant. These secondary metabolites are collectively known as cannabionoids and responsible for the pharmacological activity of plant. The affinity of cannabidiol is more towards TRPV1 than cannabinoid receptors [73] because of which its actions are more similar to capsaicin *i.e.* analgesic effects and anti-inflammatory [74, 75]. Other evidence by presented by studies [73], which claim cannabidiol to be a full agonist of TRPV1 as it increases intracellular free Ca^{2+}, by inhibiting the binding of [3H]-RTXin hTRPV1-HEK293 cells at micromolar concentration. The analgesic action of cannabidiol seems to be linked with some other in-vivo effects [76].

3.5.8. Drimanial and Polygodial

Drimanial and Polygodial are obtained from the bark of *Drymis winteri*, which is a plant indigenous to Brazil and there it has been used as folk medicine in treatment of many inflammatory disorders along with its culinary uses. These two unsaturated 1,4-dialdehyde sesquit-erpenes compounds also show similar effects to capsaicin *i.e.* anti-allergic, anti-inflammatory, and anti-nociceptive effects [77, 78]. Additionally, in the rat spinal cord membranes, they displaced the specific binding of [3H]-RTX. Similarly, same compounds increases the intracellular calcium levels in cultured rat TG neurons and also enhances Ca^{2+} uptake in rat spinal cord synaptosomes [79].

3.5.9. Allicin

Allicin is a garlic derived compound which is well Known for its various remedies against arthritis and pain, and for its antimicrobial properties. This organosulfur compound is identified as activator of TRPV1 current in only that DRG neurons which are capsaicin-sensitive but not in the ones which are insensitive [80, 81]. The volatile compounds found in the garlic bulb, which acts as TRPV1 agonists, are actually sulphur containing compounds *i.e.* DAS (diallyl sulfide), DADS (diallyl disulfide), and DATS (diallyl trisulfide) [82].

3.5.10. Curcumin

Curcumin is the principle natural phenol product found in turmeric which is responsible for its yellow color. In south-east Asia, turmeric is extensively used for culinary purposes and known to have analgesic properties. It was identified that curcumin shows antagonism on TRPV1 current induced by capsaicin [83, 84], which in turn inhibits pain hypersensitivity mediated by TRPV1. Being a chemo-preventive agent, curcumin inhibits the activity and expression of COX-2 in various GI (gastro-intestinal) cell lines [85].

3.5.11. Allyl isothiocyanate

Allyl isothiocyanate (mustard oil or AITC) is a natural compound found in mustard, known for its pungency and medicinal values. A study in TRPA1 knockout mice indicates that allyl isothiocyanate activates TRPV1 current directly, in a TRPA- independent manner.

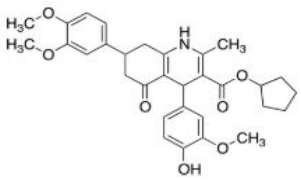
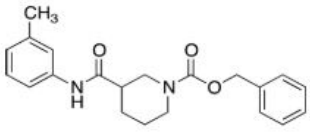
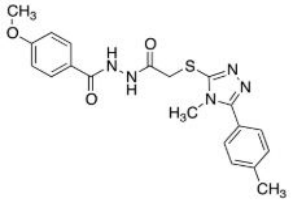
3.5.12. Yohimbine

Yohimbine is obtained either from the the bark of *Pausinystalia yohimbe* or root of Rauwolfian tree. Previous literature showed that this indole alkaloid has been used as aphrodisiac and later on, it was used to treat erectile dysfunction. Being a naturally obtaine-dalpha adreno-receptor antagonist, it is often used in characterization of MOA of drugs action on alpha adrenoreceptors. Recent studies found its inhibitory activity on Na^{+} channels and TRPV1 channels in a dose-dependent manner. The prevention of activity of action potential on dorsal root ganglion neurons by capsaicin or current injection was observed by administering yohimbine which indicates its use as pain modulator.

Table 4: Different compounds showing their action on TRPV1 channel with their mechanism of action.

Compound	Type of Cancer	Model/Cell Line Used	Possible Mechanism	Outcome	Reference
1. AMG9810 (TRPV1 Antagonist)	chemotherapy induced peripheral neuropathy	HEK293 cell culture	Paclitaxel activates TLR4 and signals downstream to this sensitize TRPV1. Increased TRPV1 signaling in cutaneous afferents may then correspond to the sensation of burning in the skin, whereas increased TRPV1 signaling in deep somatic tissue afferents may cause the deep aching and cramping, reported by CIPN patients	TRPV1 Antagonist can be used to treat CIPN	86
2. Capsaicin	Colorectal Cancer	HCT116 cells	--the activation of P53, mediated the pro-apoptotic role of TRPV1 in CRC. --TRPV1 increased Ca2+ influx and activation of calcineurin which plays a significant role in apoptosis	TRPV1 agonist like capsaicin can be used to treat CRC	87
3. Capsaicin	Breast Cancer	SUM149PT cells (model system for triplenegative inflammatory breast cancer, the most aggressive breast cancer subtype.)	An increase in calcium inside the cells by the stimulation of TRPV1 with its agonist, shows inhibition to cell proliferation	TRPV1 targeting can be used in breast cancer.	47
4. Se + Cisplatin	Breast Cancer	MCF-7 breast cancer Cells	Se & cisplatin had an apoptotic effect on MCF-7 breast cancer cells, which might be related to up-regulation of apoptosis,intracellular ROS production, and the activation of caspase 3 and caspase 9 by down-regulation of overload Ca2+ entry.	Combination of Se and cisplatin can be used as a supplement in anticancer therapy.	25
5. Cisplatin+Alpha Lipolic Acid (ALA)	Breast cancer	MCF-7 breast cancer Cells	With the increase in intracellular calcium concentration due to TRPV1 pathway-activation such changes occurs: Apoptosis, mitochondrial membrane depolarization, reactive oxygen species (ROS) production, lipid peroxidation, PARP1, caspase 3 and 9 expression levels are increased	Apoptosis and oxidant effects of Cispshowed an increase by TRPV1 channelsactivation, but ALA treatment further increased its action on the values. Combination therapy of Cisp and ALA could be used as an effective strategy for breast cancer treatment.	88
6. Doxorubicin (DOX) + Melatonin (MEL)	Breast Cancer	MCF-7 human breast cancer cells	Down-regulation of intracellular calcium due to activation of TRPV1 shows apoptosis and increase in the oxidative stress.	Possible use of MEL alongwith DOX as a chemotherapy in the future.	89

7. 5-Fluorouracil (5-FU)	Breast Cancer	MCF-7 human breast cancer cells	mitochondrial membrane depolarization and levels of apoptosis, and the caspase 3, caspase 9 and PARP1 expression levels increased are up-regulated by TRPV1 channel sactivation as a result of increase in intracellular calcium.	Use of 5-FU alone (without Hypericum Perforatum) can be used to treat breast cancer	90
8. MRS1477 (a dihydro-pyridine derivative and a positive allosteric modulator of TRPV1)	Breast Cancer	MCF-7 human breast cancer cells	--	--	91
8. Capsaicin	Osteosarcoma	Human osteosarcoma MG63 cells	Capsaicin induced the activation of AMPK (adenosine 5'-mono-phosphate-activated protein kinase), C-jun N-terminal kinase (JNK) and p53 effectively causes cell death in human osteosarcoma MG63 cells via the activation of TRPV1-dependent (mito-chondrial dysfunction, and overproduction of ROS and JNK) and TRPV1-independent (AMPK-p53) pathways.	Capsaicin can be used in osteosarcoma	57
9. Fibulin-5	Colorectal cancer	--	Upregulation of fibulin-5 caused induction of cell apoptosis andROS production through Akt and ROS/MAPK signaling pathways by downregulation of TRPV1	--	92
10. Curcumin	Colon cancer	F344 Rats	seem to act strongly via inhibition of arachidonate metabolism and through reducing cell proliferation and inducing apoptosis.	Being a pleiotropic agent, it acts on various pathways to treat cancer.	93
			(Also, it acts on TRPV1 signaling pathway to produce nociception.)		83
11. Resiniferatoxin	Canine bone cancer pain	Dogs	Being an analog of capsaicin, it shows nociceptive affect as well as cytotoxicity through an increase in calcium influx through TRPV1 signaling pathway	Human clinical trials are proposed to check its safety and efficacy measures.	94
12. Polyisoprenoids from Nypa Fruticans leaves	Colon cancer	WIDR Colon Cancer Cells	suppressing COX-2 expression	--	95
	Sciatic Neuropathies	sciatic crush injury rat models	Antinociceptive and Anti-Inflammatory Effects by Suppressing TRPV1		96
13a. Citrus Limonoids	Breast cancer	Human Breast cancer line MF7 cells	Shows apoptosis by cytotoxicity	Possible use in cancer	101

13b. Citron	Rosacea	Normal human epidermal keratinocytes (NHEKs) derived from neonatal foreskin	On the induced TRPV1 (on keratinocytes) mRNA and protein levels suppressed by citron seed or unripe citron seed oil	Citron essential oils possess both anti-inflammatory and anti-angiogenic properties	102
14. Piperine	Breast cancer	HER2-overexpressing breast cancer cells	Piperine strongly inhibited proliferation and showed apoptosis induction through activation of caspase-3and cleavage of PARP	Use of piperine in treatment of cancer	97
		whole-cell patch-clamp electro-physiology	TRPV1 desensitization		62
14. Ginsenosides (TRPV1 antagonist)	--	HaCaT cells	GRg1 blocked intracellular Ca2+ by both proton and capsaicin activation in a TRPV1dependent manner. GRg1 also showed inhibition in the expression of NF-κB and COX-2 transcriptional activity induced in keratinocytesby capsaicin. Red ginseng compounds shows various anti-cancer mechanisms like angiogenesis inhibition, paraptosis/apoptosis induction, and cell cycle arrest.	Ginseng can be used in inflammatory cancer.	98
15. Spilanthol + 5-FU	Chemotherapy induced intestinal mucositis	Swiss mice with 5-FU induced intestinal-mucositis	spilantholattenuates the intestinal mucositis induced by 5-FU by suppressing the inflammatory mediators associated with it.	Use of spilanthol along with 5-FU in chemotherapy.	99
16. Compound 1  Compound 2  Compound 3 	Sprague-Dawley rats with tactile allodynia from inflammatory pain.	Topically on induced tactile allodynia (by intra-plantar carrageenan)	These 3 compounds activate capsaicin receptor and show anti-nociceptive properties which were faster and longer lasting than capsaicin itself.	Possible use of these 3 compounds in treating inflammation and in cancer as it activates TRPV1.	100

4. CONCLUSION

TRPV1 ion channels show plethora of actions in the organisms where the major ones are anti-nociception, anti-allergic, anti-inflammatory, and anti-carcinogenic. Being activated by capsaicin, it is also known as capsaicin receptor and its main mechanism of action is to perceive or sense different stimuli and then, collectively transduce them as calcium-based signals. This intracellular calcium plays a significant apoptotic role in the oncogenic cells and show anti-cancer activity. Studies like [94] explained the positive action of resiniferatoxin, a capsaicin analog, in the treatment of bone cancer pain in the dog model. Therefore, despite capsaicin, which is obtained from red chillies, there are other synthetic and natural compounds as well which show their activity on TRPV1 channel. For instance, synthetic compounds like, 5-FU and Fibulin-5 are known to treat breast and colon cancer, respectively [90, 92]. Whereas, piperine, cannabidiol and curcumin are some of natural products which show TRPV1 modulation as one of their major mechanisms in the body. Its role as a potential anti-inflammatory target has been claimed when it showed a significant decrease in the factors causing inflammation [39-44]. After targeting TRPV1 by various compounds,[1] implicated use of TRPV1 modulators as a passible approach in the treatment of cancer. Amalgamating the above studies, it is hypothesised and proposed that TRPV1 targeting natural products can be used in the treatment of inflammatory cancer.

Conflict of interest

None declared

5. REFERENCES

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