

**Systematic Review****Garlic Activate TRPA Receptor as a potential therapeutic target in skin related diseases****Muhammad Aqib Saeed¹, Shahnai Basharat¹, Momina Shahid^{1*}, Aimen Zafar¹, Hifza Noor¹, Asifa Saleem², Imtiaz Ahmad Rana¹, Tehreem Jamil¹**¹University Institute of Diet and Nutritional Sciences, The University of Lahore, Lahore, Pakistan²Institute of Food and Nutrition Science, Pir Mehar Ali Shah Arid Agriculture University, Rawalpindi, Pakistan**ARTICLE INFO****Key Words:**

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mominamalik14@yahoo.comReceived Date: 14th May, 2022Acceptance Date: 5th June, 2022Published Date: 31st July, 2022**ABSTRACT**

Due to its strong flavour, garlic has long been a staple in cuisines all over the world. When chopped and put on the tongue or lips, raw garlic triggers unpleasant burning and prickling sensations by unknown processes. The study showed that temperature-activated ion channels TRPA1 and TRPV1, which are a part of the (TRP) transient receptor potential, are activated by raw garlic. The molecule that activates TRPA1 and TRPV1 is allicin, a volatile compound found in fresh garlic. Allicin and diallyl disulfide, two organosulfur chemicals that give garlic its distinctive flavour and spicy aroma, are produced by the Allium genus. Allium extracts have been shown to provide a variety of health advantages, including hypotensive and vasorelaxant properties. It's intriguing that allicin and DADS share a structural affinity for allyl isothiocyanate, which triggers pain and inflammation by activating TRPA1.

INTRODUCTION

Garlic is a member of the plant genus Allium has various sulfur-based natural compounds. One of which is allicin (2-propenyl-2-propene thiosulfate), found particularly in the cloves. When the bulb is crushed, allicin is produced in result of a chemical reaction mediated via vacuolar enzyme, alliinase, which catalyzes the process [1]. Aqueous solutions of allicin and other thiosulfates have a short half-life, resulting in organosulfur bioproducts such as allylsulphides, ajoene, and dithiane, Intriguingly, the structure of these chemicals is quite similar to that of isothiocyanates, which are the spicy substances found in wasabi, yellow mustard, and other Brassica plants [2].

Garlic has been used as an herbal remedy for treating a variety of diseases for many centuries, including hypertension, high cholesterol levels and thrombosis (blood clotting). On the other hand, activation of the TRP channel family (TRPV1 and TRPA1, respectively) is responsible for the excitation of primary sensory neurons by both capsaicin and AITC [3]. Allicin also has antifungal and antibacterial properties. Allicin triggers the activation of TRPA1 and TRPV1. The creation of allicin from compounds by the enzymes conjugase, which is in charge of allicin production, results in the strong aroma that is released when garlic is crushed. 2-propenesulfenic acid is

created when allicin is degraded, and it subsequently binds to free-radical and neutralizes them [4].

Structure and function of TRPA1 channels

The N-terminus of TRPA1 channels has a considerable length of ankyrin repeats, as well as calcium-sensitive regions in the EF-hand motifs and the S4 membrane segment. TRPA1 valves have a long transmembrane receptor repeat region within their N-terminus. The flexible ankyrin domains may provide the structural basis for protein-protein interactions, according to some theories [5]. Numerous stimuli, including as changes in osmotic pressure, higher and lower temperatures, and irritants that are both natural and synthetic, have been shown to activate TRPA1 channels. It has been postulated that the creation of a noncovalent C422-C622 disulfide bond is responsible for the TRPA1 activation in response to sulphide [6]. Unsaturated fats, low or high pH, and non-reactive compounds that attach with non-covalent contacts have also been demonstrated to trigger TRPA1 valves in vitro. The responses of TRPA1 channels are integrated by activating stimuli such as temperature, light, bacteria toxins, mechanical, and chemical stimuli, among others [7]. TRPA1 channels found in the brain appear to be involved in neurodegenerative and inflammatory autoimmune disorders and Alzheimer's disease, according to recent research, these findings suggest that TRPA1 channel antagonists plays role in the treatment of these diseases [8]. According to the researcher, the channel is extremely Ca^{2+} porous and that bivalent cations penetrating the channel contributing the channel regulation, which is characterized by early raise followed by insensitivity. The nutrient myo-inositol-1, 2, 3, 4, 5, 6-hexakisphosphate maintains an unexpected novel ligand-binding site as well as an unusual C-terminal coiled coil (phytic acid, IP6). They conclude from this that IP6 and other endogenous solubility intracellular ligands are necessary to maintain the region's agonist-receptive status [9]. Removal of IP6 caused by the inflow of Ca^{2+} after channel activation might operate as a molecular kill switch, causing the channel to become inactive [10, 11].

TRPA1 catalysts

In evaluation with different chemoreceptors, which can be normally stimulated via ligands with as a substitute conserved structure, a completely unique characteristics of a TRPA1 that are activated through plenty of structurally unrelated compounds [12].

Exogenous compounds

Garlic has an active component known as thiosulfate, which is important for the pungent and spicy scent, when its stem broke after some hours; the subcellular enzyme alliinase converts the alliin into allicin. It is transformed into more steady compounds like diallylsulphide (DAS),

diallyltrisulfide (DTS) and diallyltrisulfide (DTS) in the same way as other highly reactive sulphur compounds (DATS). These chemicals activate TRPA1 valves results in the production of pro-inflammatory neuropeptides and the sense of pain and inflammation [13].

Effects of garlic mediated by TRPA1 channels

The garlic compound "ajoene" enhances the effects of several TRPA1 channel agonists in the cells. Capsazepine, a TRPA1 channel antagonist reduce the effects of diallyl compounds. The nerve terminals in the mouse isolated skin were stimulated by DMTS, which resulted in the production of somatostatin. Skin samples anatomized from TRPA1 channel knockout mice were shown to be devoid of the effect. In vitro, DMTS reduced the TRPA1 channel and SSt4 receptors-dependent mechanical hyperalgesia brought on by mild thermal injury. However, in mouse carrageenan-induced paw infection, repeated intravenous administration of DMTS decreased nociception, edoema development, and myeloperoxidase activity [14, 15].

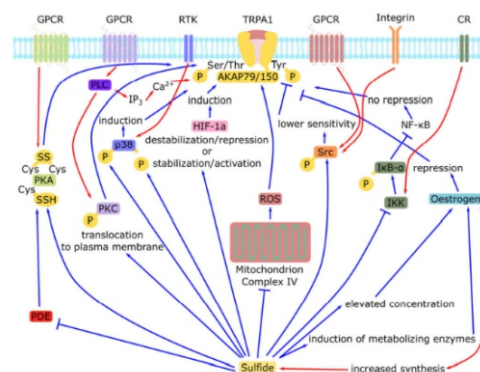


Figure 1: Potential ways via which sulphide modifies TRPA1 function or expression. Hormones, reactive substances, transcription factors, and signaling kinases all influence how the TRPA1 ion channel is activated or expressed.

p38 MAPKs

An improvement in the responsiveness of TRPA1 gates to pharmacological substances and membrane stretch characterizes the odontoblast cells' response to TNF treatment. The effect was facilitated through the stimulation of TRPA1 channels by MAPKs 38 (p38), which was induced by the drug [16]. There may be very little evidence that sulphide chemicals can increase phosphorylation and p38 kinase enzyme activation. By stimulating the p38 MAPK pathway, NaHS increases the glucagon like peptide-1 (GLP- 01) synthesis in mice. In human monocytes, the p38 protein activation as a consequence of NaHS was observed [17]. Similar to cisplatin, garlic-derived DATS reduces oxidative stress in NCI-H460 human lung cancer cells, which is caused by cisplatin exposure [18].

AMP-activated protein kinase (AMPK)

According to its function, AMPK serves as an energy sensor in cells that are triggered by increasing AMP (reduces ATP) concentrations. AMPK is triggered by either activation or Ca²⁺ signals via the Tracks protein kinase. In recent years, it has been proven that AMPK is involved in controlling cell autophagy, as well as atherosclerosis, inflammatory illness, and cancer. TRPA1 channels in DRG neurons were downregulated by AMPK, as shown by a reduction in the quantity of membrane bound TRPA1 peptide in sensitivity to insulin and an increase in the amount of TRPA1 antigen when AMPK action was reduced [19, 20].

IkB kinase complex (IKK)

IKK may be, is responsible for the phosphorylation and subsequent degradation of the crucial and ubiquitous IL-2, which results in the activation of its inhibitory protein IB-. Data from nociceptor neurons that have been genetically altered to lack IKK reveals that the kinase complex is responsible for the suppression of TRPA1 channel expression [21]. Both inorganic sulphide and organic polysulfides seem to influence IKK, which may have an impact on the expression of TRPA1 channels in a variety of ways. Sulfide has only been studied in non-neuronal tissues to understand how it regulates the IKK complex. According to fig.2 in primary effusion lymphoma cells, garlic-derived DATS induced apoptosis by inhibition of the IKK pathway, limiting proteasome-driven degradation of IB and therefore decreasing nuclear factor-B (NF-B). A similar impact of DADS was seen in rat hepatocytes that had been exposed to carbon tetrachloride [22]. Inorganic sulphide was shown to inhibit NF-B signaling via modulating IKK in rat cardiomyocytes subjected to hemorrhagic shock, which was previously reported in humans. The sulfide-releasing diclofenac may be able to inhibit breast cancer-induced osteoclast development by a mechanism that is like that of diclofenac [23].

Estrogen

The method by which estrogen modulates TRPA1 channels, as shown here, is extremely disputed and based on a small body of data, only one study has been published on the ovariectomy-induced death of rat hippocampus and DRG neurons, which was shown to be partially dependent on Ca²⁺ influx mediated by TRPA1 channels [24]. In addition to the well-known effect of estrogen on the expression of sulfide-producing enzymes, some evidence suggests that sulphide may also influence estrogen production or metabolism. Eight weeks of administration of the sulphide precursors cysteine to rats resulted in a rise in the serum concentrations of 18-oestradiol in the blood. It has been demonstrated that DAS interacts with the internal intrinsic combination of drugs receptor and stimulates the synthesis of sulfotransferases that break down estrogen. Although this had no effect on the serum estrogen levels, it

did influence the levels of exogenously injected hormones [25].

TRPA1 and TRPV1 Collaborate to Cause Skin Disorders

In addition, genetic deletion of TRPA1 in mouse models of pruritus and psoriasis prevented scratching and improved skin lesions, suggests that the channel regulates itch transmission to the central nervous system as well as pathophysiological changes in the skin. Moreover, the involvement of TRPV1 in skin illnesses has been examined, with results indicating that both channels are implicated in IL-31-induced itching; indeed, TRPV1 or TRPA1 pharmacological inhibition as well as ROS scavengers were shown to reduce itching in mouse models [26]. As of now, it is unclear if the TRPA1 and/or TRPV1 are involved in the pathogenesis of skin irritation (ACD) models. TRPA1 (but not TRPV1) genetic deletion or pharmacological blockade reduced ACD symptoms and dopamine independent scratch behavior [27]. Note that oxidative stress-induced itch is controlled by TRPA1 and is not controlled by TRPV1, but chloroquine and BAM8-22 both caused TRPA1-dependent scratching behavior that was not controlled by TRPV1. When comparing damaged skin samples from Atopic Dermatitis (AD) patients to the controls (healthy ones), the activation of TRPA1 in dermal sensory nerves throughout the disease was shown to be significantly higher than in controls. As a result, TRPA1 is not only required as a sensor for pruritogens, but it is also required for the maintenance of Atopic Dermatitis. Transient receptor potential channels are widely expressed in a variety of skin cell types, including epithelial, mast cells, skin extremity cells, nerve cells, and lymphocytes. They have a variety of functions, including those related to the skin barrier, hair growth, wound healing, and itching [28]. Among the possible targets for itching relief are TRPA1, TRV3, TRV4, and, to a subsidiary extent, TRPV1 and TRPM8, as well as TRPA1. Human psoriatic epidermis biopsies show elevated TRPA1 expression, which is compatible with the condition [29]. Skin-targeted, gain-of-function Trpv3Gly573Ser transgenic mice demonstrate scratching behavior as a result of the gain-of-function mutation. Lesional keratoderma 105 has revealed human TRPV3 mutations, and post-burn pruritus patients exhibit increased TRPV3 expression. Additionally, genetic Trpv4 deletion lowers itching in animal studies of chronic itching, and TRPV4 is overexpressed in skin biopsy specimens from people with chronic pruritus [30]. It has also been reported that a TRPM8 antagonist (menthoxypropanediol) cream may reduce human itching. People with atopic dermatitis can gain from of the Adrenoceptor blocker PAC-14027, which is now being studied in phase III of clinical trials. It lessens itch in people who are affected by it and enhances skin barrier functions. CNS stimulation in TRPV1-Au31

optogenetic mice stimulated TRPV1-expressing neurons, triggering a mucosal immune response, which in turn caused keratinocyte antimicrobial reactions and drew neutrophils to the skin. If this finding is confirmed in humans, it is possible that individuals who are treated with topical TRPV1 inhibitors will be more prone to cutaneous bacterial pathogens infections. TRPV4 has indeed been suggested as a promising receptor in rosacea, while TRPV1 has been associated to psoriasis [31]. Eyedrops containing a TRPM7 agonist, which moisturizes the cornea, may be helpful for patients with dry eye disease [32]. The TRPV4 inhibitor, HC-067047, was demonstrated to be beneficial in preventing scarring (endothelium opacification) after alkaline burn injury in animal studies. Finally, it has been demonstrated that intraocular TRPV1 antagonist injections can treat allergic conjunctivitis. [33, 34].

TRPA1's Function in Skin Pathology and Anatomy

TRP channels, which are mainly permeable to calcium and serve as cell membrane sensors in a variety of physiological capacities, including pure sensory activities like pain perception and thermal sensation, as well as bodily systems like electrolyte balance and a plethora of other functions like muscle movement and vagal control [35]. However, it is believed that they are crucial for the creation and upkeep of venous calcium homeostasis as well as for the control of membrane trafficking. [36]. TRPs are recognized as distinct polymodal nociceptors because alterations in the intracellular space, as well as a range of outside and internal tactile stimulation and chemical mediators, directly influence their gating. [37].

Garlic and skin health

Garlic, a member of onion family, is among the most well-researched and best-selling herbal treatments, and it has been used to cure a wide range of health issues for hundreds of years [38]. Enzymes (for example, alliinase), chlorine substances such as alliin, and chemicals formed enzymatically from compounds (for example, allicin) are among its components [39]. There are four kind of garlic preparations that can be purchased: aged garlic extract, dried garlic powder, and raw garlic juice (RGJ, HGJ) (AGE). Although there are pharmacological challenges with different types of garlic preparation, AGE is the most advantageous of the four [40]. By immersing or whole sliced cloves of garlic in an ethanol solution for varied amounts of time, one can produce garlic extract, which has a concentrated flavour [41, 42].

TRPA1 and Skin Disorders

Allergic contact dermatitis and atopic dermatitis

A damaged skin barrier, a growing immunological response affected by T helper 2 (Beginnings) cells and related substances including cytokine (IL-13, Interleukin-8, plus IL-13, and an inflammation influenced by neutrophils are the

hallmarks of atopy (Fd) and allergic skin reactions. [43]. In the cells called of dorsal root (DRG) cells from Vascular dementia (AD) rats, TRPA1 expression was elevated [44]. However, TRPA1 was only overexpressed in DRG neural cells in animal studies of ACD, whereas non-neuronal cells in such animals did not exhibit elevated channel expression [45]. This collection of evidence shows a complex interaction between TRPA1+ mast cells and dermal afferent neurons in the Partition inflammatory milieu underlying chronic itch in Alzheimer's disease [46].

Psoriasis

The most common chronically agitated skin disorder that results in erythema, thick skin, and scaling is psoriasis [47]. Between 60 and 90 percent of the patients are pruritic. New research reveals that the aetiology of psoriasis may be related to nociceptive sensory nerve endings. The pathophysiology of the disease involves these nerve terminals in a variety of ways [48]. It is noteworthy that several investigations have demonstrated increased C-fiber afferent fibers in the epidermal of individuals with psoriasis skin lesions [49]. Furthermore, there was an inverse correlation between the presence of higher neuropeptide levels in psoriasis patients' plasma and the intensity of their condition. [50]. Moreover, cutaneous denervation has been shown to reduce skin inflammation in individuals with psoriasis as well as in mice suffering from it as dermatitis [51]. Similar findings were achieved in psoriatic skin from human participants who had their TRPA1 and TRPV1 genes over-expressed, which was similar to the results obtained in mice [52]. Pharmacological inhibition or genetic deletion of TRPA1 in mice might aggravate the dermatitis associated with psoriasis as well as nicotine and itching behavior, indicates that TRPA1 may have a protective role in the disease [53].

Cutaneous T-Cell Lymphoma

Mycosis fungoides and Sézary syndrome are the most frequent scientific presentations of primary epidermal lymphoproliferative disorders, among which cutaneous T-cell lymphocytes (CTCL) are the most common clinical manifestations [54]. The degree of pruritus in these patients may be partially explained by their switch to Th2-type immunity, in which neoplastic cells release more Th2-linked mediators such as IL-4 and IL-31. However, current evidence indicates that TRPA1 is an important mediator in the emergence of CTCL-associated itch. [55].

Other itchy skin conditions or systemic illnesses

Scabies is a common skin illness influenced by itching and pruritus. It is caused by the mite *Sarcoptes scabiei hominis*, which is a contagious parasitic infection. Quasi itching receptors such TRPA1, TRPV1, and the proteolytic enzymes receptor 2 (PAR2) are overexpressed in scabies sufferers' skin, according to research [56]. In vitro, TRPA1

sensitization was heightened by TRG5 stimulation by BA due to increased signal transduction via G, kinases, and calcium. Further evidence for the major factors that contribute of TGR5 and TRPA1 in BA-induced itch was provided by the finding that TRPA1 antagonists lessened the severity of mice overexpressing TRG5's increased spontaneous scratching activity [57]. Although channel expression did not significantly correlate with eosinophil dermal infiltration or the severity of pruritus, TRPA1 overexpression was discovered in the epidermis of patients with bullous pemphigoid, a rare auto-phagocytic disease characterized by excessive pain, when compared to healthy skin [58]. The itching that follows a burn damage also results from physical causes and is a different source of pruritus. According to recent studies, those with itchy burn scars have higher amounts of the mRNAs TRPA1 and TRPV4 in their skin [59]. However, further research is required to determine the involvement of TRPA1 in the development of burn-associated itching.

Therapeutic Perspectives and Future Directions

It has been shown that TRPA1 is involved in chronic neuropathic and cancer pain [60]. On the other hand, present knowledge of the etiological functions of TRPA1 in the skin is incomplete and requires more research. This study has demonstrated that TRPA1 may have a wide range of functions in a number of physiologic and pathologic skin diseases. A growing body of research suggests that TRPA1 is crucial in the histamine-independent itching that occurs frequently in chronic autoimmune skin conditions like Hypertension, organ failure, or neoplastic diseases like cutaneous T-cell lymphoma. As a result, these conditions make ideal targets for research into TRPA1-targeting medications in people. It has been demonstrated that crocophiline may lessen the formation of chemical mediated inflammatory sensitivities in mice by desensitising TRPA1-peptidergic nerve terminals [61]. The sensitivity of sensory neurons that express TRPA1 and TRPV1 has been shown to be decreased by the combo of alkahtani hcl and fluticasone propionate [62]. After being exposed to isopetasin or parthenolide, the TRPA1 channel and the TRPA1-expressing cells experience a dose-dependent neuronal desensitisation, which could explain why the two plant extracts reduce pain and neurogenic inflammation [63, 64].

For instance, TRPA1 proteins have been found in tumor cell lines, albeit it is yet unknown what role TRPA1 plays in melanoma in vivo. TRPA1 is required for the pain associated with skin malignancies or associated therapy to be signaled [65]. This includes pain related to photodynamic therapy, which is effective in treating non-melanoma skin cancer, and pain related to dacarbazine-induced discomfort in melanoma [66, 67]. Additionally, it could be interesting to

look at TRPA1 activity in relation to the discomfort brought on by infectious or autoimmune skin conditions like vasculitis vulgaris. Finally, mounting evidence points to a role for TRPA1 in the fibrosis development associated with systemic diseases. Given the lack of effective treatments for fibrogenic skin conditions (such as scleroderma) and tissue repair, it is important to investigate if TRPA1 plays a role in fibrosis in these situations [68].

CONCLUSION

This study concluded that Garlic Activate TRPA Receptor as a potential therapeutic target in skin related diseases. Allium extracts have been shown to provide a variety of health advantages, including hypotensive and vasorelaxant properties. It's interesting to note that allucine as well as DADS have a structural affinity for allyl isothiocyanate, which causes inflammation and pain by activating TRPA1.

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