Scientific Research Publishing

Modern Research in Inflammation, 2026, 15(1), 1-20
https://www.scirp.org/journal/mri
ISSN Online: 2169-9690
ISSN Print: 2169-9682

Cutaneous Neuro-Immune Interactions in Chronic Itch and the Role of TRP Channels in Emerging Therapies

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How to cite this paper: Felipes, R.S., Meihofer, A., Patel, A., Asemi, N., Depina, J., Kalidindi, S., Pomerantz, E.R. and Frasier, K. (2026) Cutaneous Neuro-Immune Interactions in Chronic Itch and the Role of TRP Channels in Emerging Therapies. *Modern Research in Inflammation*, **15**, 1-20.
https://doi.org/10.4236/mri.2026.151001

Received: August 7, 2025
Accepted: February 24, 2026
Published: February 27, 2026

Abstract

The interplay between the cutaneous nervous and immune systems plays a notable role in the pathogenesis of chronic itch, a debilitating symptom associated with conditions such as atopic dermatitis, psoriasis, and prurigo nodularis. Recent advances in neuro-immune biology have discovered the importance of transient receptor potential (TRP) channels, particularly TRPV1, TRPA1, and TRPV4, as critical mediators in the transmission and modulation of pruritic signals. These ion channels, expressed on sensory neurons and keratinocytes, serve as molecular conduits linking environmental, immunological, and neuronal stimuli to itch perception. Dysregulated TRP channel activity has been implicated in the amplification of chronic itch through mechanisms such as mast cell degranulation, the release of pro-inflammatory cytokines, and sensory nerve hypersensitization. Emerging therapies targeting these channels offer a novel approach to interrupting this pathological crosstalk. TRPV1 and TRPA1 antagonists have demonstrated efficacy in preclinical and early clinical studies by attenuating neuronal excitation and inflammatory cascades, while TRPV4 modulators hold promise in mitigating itch associated with mechanical and thermal stimuli. Additionally, the downstream signaling pathways of TRP channels, including the release of calcitonin gene-related peptide (CGRP) and substance P, present further therapeutic targets for modulating neurogenic inflammation and sensory input. Beyond pharmacologic interventions, insights into neuro-immune interactions have guided the de-

velopment of biologics that dampen cytokine-driven pruritus, including IL-31 and IL-4/IL-13 inhibitors. The exploration of cutaneous neuro-immune interactions and TRP channel biology has unveiled transformative opportunities for understanding and treating chronic itch, highlighting a promising avenue for addressing the unmet needs of patients suffering from this distressing condition.

Keywords

Chronic Pruritus, Transient Receptor Potential Channels, TRPV1, TRPA1, TRPV4, Atopic Dermatitis, Cytokine-Mediated Itch, Psoriasis, Targeted Therapies, Biologics

1. Introduction

Chronic itch, defined as symptoms persisting for more than six weeks, is a debilitating manifestation of various inflammatory and neuropathic conditions [1]. The lifetime prevalence of chronic pruritus is approximately 22% across multiple diseases [2]. Conditions such as atopic dermatitis (AD), psoriasis, and prurigo nodularis significantly contribute to pruritus. AD affects approximately 9.9% of individuals over their lifetime, while psoriasis impacts around 3% of U.S. adults, with a slightly lower prevalence of 2.5% observed in Asian Americans [3] [4]. Though less common, prurigo nodularis has a prevalence of about 0.1%, with a notable one-year mortality rate of 5.4%, underscoring its clinical severity [5]. These statistics highlight the substantial burden of chronic itch on public health and emphasize the need for more effective, targeted treatments to mitigate its impact on patient well-being.

Beyond the direct impacts experienced by the disease, chronic itch can significantly impact a patient's quality of life and clinical outcomes [6]. Sleep disturbances, frequent medical visits, and psychological distress, including negative self-image, are among the major consequences of chronic pruritus. Current treatment strategies remain limited and face challenges due to the complex and multifactorial pathophysiology underlying chronic itch [7]. Treatment progression often involves prolonged and costly trial and error, reinforcing the urgent need for therapies specifically targeting the underlying mechanisms of chronic itch.

The nervous and immune systems are central to itch pathophysiology, with transient receptor potential (TRP) channels playing pivotal roles in sensory signaling. Specifically, TRPA1, TRPV1, and TRPV4 have been studied in the pathology of pruritus and often are primary or downstream targets of itch mediators [8] [9]. TRPV1 and TRPA1 are implicated within the itch signaling pathway, with TRPV1 activation contributing to the release of pro-inflammatory cytokines [9]. Similarly, TRPV4 is a therapeutic target due to its role in itch sensation [10]. Developing a thorough understanding of the molecular, cellular, and epidemiologi-

cal variables underlying these complex pathways is fundamental to developing targeted therapies to address the current clinical gaps in chronic pruritus treatment.

This review focuses on the role of TRPV1, TRPA1, and TRPV4 in the pathophysiology and treatment of chronic itch. These TRP channels have become key targets in the pharmaceutical industry. For instance, Carvajal *et al.* extensively review treatments investigating TRP channel modulators and therapeutic targets, highlighting their potential to improve chronic pruritus management [11]. This paper aims to enhance the understanding and inform future clinical management of this affliction by providing a detailed and updated review of the mechanisms that govern chronic pruritus.

2. Pathophysiology of Chronic Itch

Evoking an itch response involves an interplay of the environment and the various cells in the epidermis, such as keratinocytes, immune cells, and sensory neurons. The sensation of an itch is sensed by cutaneous nerve fibers known as pruriceptors, which are comprised of C fibers that respond to histamine, pruritogens, and cowhage, a product of the spicules of a bean plant known as *Mucuna pruriens* [12]. The pathophysiology of cutaneous itch is linked to an imbalance of helper-T cells, increased IgE levels, or loss of skin barrier integrity. The skin barrier theory suggests that mutations of filaggrin, a protein involved in keratinocyte binding and epidermal structure, increase permeability, allowing allergens and pathogens to penetrate easily [13].

Studies have shown that dry skin and barrier dysfunction, such as in AD, lower the itch threshold by increasing intraepidermal-nerve fibers and promoting sensitization through interleukin (IL)-33, which is produced and secreted by keratinocytes [14]. Heightened sensitivity leads to an exaggerated itch response to environmental, immunologic, and neuronal stimuli that would not typically induce itching in non-sensitized skin. A compromised skin barrier also facilitates pathogen entry, further exacerbating the T-cell activation and IgE-mediated itch response.

Beyond external triggers, endogenous factors such as pH changes, lipid alterations, and "stress peptides" also contribute to itch by activating receptors on immune cells and nerve endings through TRP vanilloid (TRPV1) channels, which in turn promote pruritus and skin barrier dysfunction [15]. Further investigation into the interactions between immune cells, pathogens, cytokines, and TRP receptors could provide deeper insight into the pathogenesis of chronic itch. TRP channels play a crucial role in itch and pain signaling by modulating downstream pathways activated by G-protein coupled receptors (GPCR) [16]. TRP and GPCR receptors are activated by various pruritogens, which drive the neuronal perception of an itch. Mast cells are key players in innate and adaptive immunity and rapidly degranulate in response to environmental insults such as allergens and pathogens [17]. During an acute itch episode, keratinocytes and local immune cells detect epidermal damage or pathogen-associated molecular patterns and release chemi-

cal mediators that trigger mast cell degranulation [18]. The subsequent release of cytokines induces vasodilation, facilitating immune cell recruitment to clear the offending agents.

Among the numerous TRP channels that modulate chronic itch, TRPV1 is one of the most well-studied. TRPV1 plays a significant role in itch mediated by histamine and indirectly affects non-histaminergic pruritus, a major pathway in chronic itch [19]. A deeper understanding of the most common TRP receptors and their ligands can advance our understanding of how they serve as molecular conduits for itch transmission, guiding more targeted therapeutics.

3. Transient Receptor Potential (TRP) Channels

TRP channels are a family of ion channels that play a vital role in sensory perception, especially in the itch sensation. Channels like TRPV1, TRPA1, and TRPV4 mainly detect itch signals. Understanding how these channels work is crucial for developing treatments for chronic itch conditions [19].

TRPV1 is a non-selective, noxious heat-sensing Ca^{2+} ion channel that recognizes algesic and pruritic molecules [10] [11] [20]. Various stimuli can activate it, including capsaicin, heat, and acidic conditions. Additionally, endogenous lipids (e.g., endocannabinoids), lipoxygenase products, and bradykinin have been shown to stimulate TRPV1 [10]. Upon activation, TRPV1 triggers a cascade of downstream inflammatory signaling molecules such as Phospholipase C (PLC), IP3, Diacylglycerol (DAG), Protein Kinase C (PKC), and NF-KB via the PAR2-mediated Ca^{2+} pathway [21] [22]. Xu *et al.* demonstrated that sophorolipid, a biosurfactant, exerts immunomodulatory effects against histamine-induced itch linked to TRPV1 channels [23]. In HaCaT cells, sophorolipid suppressed both the histamine-activated PLC/IP3R and capsaicin-induced signaling pathway by reducing intracellular calcium levels. Immunofluorescence and molecular docking analysis revealed the ligand-receptor interaction between sophorolipid and TRPV1, indicating its inhibitory effects [23]. The blockade of TRPV1 channels provides potential therapeutic interventions in mitigating chronic itch.

TRPA1 is a thermoresponsive cation channel involved in cold sensations in neuronal and skin cells. It contributes to neurogenic inflammation through exogenous (e.g., chloroquine, cowhage) and endogenous mediators (e.g., IL-13, IL-33, leukotriene B4) [19] [22] [24]. TRPA1 channels are susceptible to Ca^{2+}, exerting bimodal effects by promoting sensitization and desensitization. Calcium mediates intracellular sensitization of TRPA1, whereas desensitization can be indirectly regulated through GPCRs, such as bradykinin receptors, protease-activated receptor 2 (PAR2), and calcitonin gene-related peptide (CGRP) signaling pathways [24] [25]. Feng *et al.* identified TRPA1 as the primary receptor responsible for the acute scratch response in experiments involving subcutaneous applications of SADBE, a hapten that activates both TRPA1 and TRPV1 [8]. Intradermal injections of SADBE in double knockout mice ($Trpa1^{-/-}/Trpv1^{-/-}$) did not produce a robust scratching behavior compared to wild-type mice. However, $Trpa1^{-/-}$ mice dis-

played a significantly attenuated scratching response, similar to that observed in the double knockout mice. SADBE-elicited scratching was not significantly reduced in the Trpv1$^{-/-}$ mice, suggesting that TRPA1 is the predominant itch receptor in acute scratching response induced by subcutaneous applications of SADBE. However, this does not underscore the involvement TRPV1 can have in generating persistent itch [8]. Exploring the distinct and complementary roles of TRPA1 and TRPV1 in mediating itch is essential for targeted therapeutic interventions.

Multiple pathways contribute to itch dysregulation involving TRPV4 channels, including aberrant thermoception, osmotic changes, ultraviolet B (UVB), and serotonin (5-hydroxytryptamine [5-HT]) induced pruritus [10] [19] [26]. TRPV4 is expressed in sensory neurons of dorsal root ganglia (DRG) and trigeminal ganglia (TG), as well as in keratinocytes, mast cells, and macrophages. In keratinocytes, histaminergic pruritogens activate TRPV4, inducing calcium influx and triggering mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) phosphorylation and downstream signaling [27]. Chen *et al.* found that UVB overexposure activates ionotropic TRPV4, an effect enhanced by endothelin-1 (ET-1) via endothelin receptors A and B [27]. This activation triggers a Ca^{2+} influx, increasing gene expression of ET-1 and further amplifying its production. ET-1 and TRPV4's interaction is relevant as ET-1 has been found to cause itch in human subjects and mice through intradermal injections [27]. Within neural tissue, Akiyama *et al.* found that 90% of 5-HT sensitive DRG displayed immunoreactivity to TRPV4 antibodies, linking 5-HT-induced itch to TRPV4 [26]. However, Akiyama *et al.* reported that TRPV4 knockout mice showed significantly reduced scratching in response to intradermally injected 5-HT, with no difference in histamine-induced scratch bouts compared to wild-type mice [26]. While TRPV4's role in itch perception is evident, inconsistencies in its involvement in histamine-induced pruritus underscores the need for further investigation.

4. Amplifying Chronic Itch

Chronic itch is a complex sensation mediated by multiple cellular interactions and signaling pathways. Mast cells, TRP channels, and sensory neurons all play a critical role in amplifying pruritus, with recent literature discussing the various mechanisms by which these elements contribute to chronic itch conditions.

Mast cells play a crucial role in initiating and amplifying itch by releasing pruritogenic mediators [28] [29]. Activation of mast cells through IgE cross-linking to FcεRI induces degranulation and the release of histamine tumor necrosis factor-α (TNF-α), IL-6, IL-4, IL-13, and IL-31, and transforming growth factor-β (TGF-β) [30]-[32]. Clinically, Zheng *et al.* noted that TRPV1 is upregulated in hypertrophic scars (HS), promoting pruritus by enhancing IL-31 expression [33]. The increased presence of mast cells and elevated IL-31 in HS tissue suggests an interplay between TRPV1 and mast cells in HS-associated itch. Additionally, sensory neurons and mast cells interact to drive pruritic responses. Histamine re-

leased from mast cells binds to four different G-coupled protein receptors (H1R, H2R, H3R, and H4R), with H1R expressed by DRG neurons [34]. Wang *et al.* demonstrated that histamine binding to H1R triggers TRPV1 activation, leading to depolarization and itch sensation. Murine models further support TRPV1's involvement in the histamine-H4R itch axis [34]. While mast cell degranulation is critical in chronic itch amplification, further studies are needed to clarify its interactions with the TRP channel family.

TRP channels play a central role in neuronal hypersensitivity and itch perception. Spinal interneurons regulate itch signals by modulating their transmission from the spinal cord to the brain [35]. BHLHB5, a neural-specific transcription factor, marks these inhibitory interneurons [16] [18]. Loss of BHLHB5 leads to the depletion of a subset of inhibitory spinal neurons, B51, which release dynorphin, a κ-opioid peptide that suppresses itch. These neurons receive direct synaptic input from TRPV1, TRPA1, and TRPM8. The TRP channels serve as primary sensory neurons, relaying counter-stimuli from the periphery [16]. Supporting this role, Sun *et al.* found that menthol's inhibitory effect on chloroquine-induced itch was absent without BHLHB5 interneurons, indicating that TRP channel-mediated counter-stimuli rely on BHLHB5 for itch suppression. Impaired inhibitory control between the BHLHB5 and TRP channels may underlie chronic itch disorders [35].

Furthermore, phospholipase A2 (PLA2) genes have been implicated in itch by directly activating TRPA1 and TRPV1, transmitting itch signals via peripheral sensory fibers. Although the exact mechanism remains unclear, Mahmoud *et al.* propose that PLA2 contributes to peripheral and central itch sensitization by stimulating signal transduction and excitatory sensory neurons [35]. PLA2 activity has been linked to itch intensity in atopic dermatitis and psoriasis, further reinforcing its relevance in chronic itch pathology. Enhancing our understanding of TRP channels in neuronal hypersensitivity and itch modulation may lead to novel therapeutic strategies to alleviate the burden of chronic itch.

5. Emerging Therapeutic Approaches

5.1. TRP Channel Antagonists

Preclinical studies have demonstrated that direct or indirect TRP channel inactivation by antagonists or modulators can significantly reduce itch behaviors in histamine-induced and chronic pruritus animal models. However, few of these compounds have advanced to clinical trials, as highlighted in **Table 1**. These compounds have been tested for topical applications and systemic treatments, but systemic delivery may lead to adverse effects in other tissues. For example, one clinical trial was discontinued in phase I due to the TRPV1 antagonist, AMG-517, causing hyperthermia in participants [36]. Limited clinical data and challenges related to administration routes highlight the need for further investigation of TRP channel antagonists.

Table 1. Emerging TRP channel targeting therapies.

Emerging TRP Channel Targeting Therapies					
Name	**Target**	**Side effects**	**Model/Species**	**Study Type**	**Reference**
Asivatrep (PAC-14028)	TRPV1 Antagonist	No significant safety issues reported	Human	Phase III clinical trial	39
SB705498	TRPV1 Antagonist	No clinically significant adverse events reported	Human	Clinical trial	41
AMG-517	TRPV1 Antagonist	Hyperthermia	Human	Discontinued clinical trial	36
Topical Acetaminophen	TRPV1 Modulator	Limited data	Human	Double blind, randomized	43
Cannabinoids	TRPV1 Modulator	Contact/irritant dermatitis	Human	Observational study	44
HC-030031	TRPA1 Antagonist	None reported	Mice	Experimental *in vivo* study	48
A-967079	TRPA1 Antagonist	None reported	Mice	Experimental *in vivo* study	49
Menthol	Inhibition of TRPA1	Irritation, blistering, burning, itching, pain, redness, swelling	Human	Observational Study	44
Camphor	Inhibition of TRPA1	Contact dermatitis	Human	Observational study	44
Crotamiton	Inhibition of TRPV4	Irritation	Mice	Experimental *in vivo* study	51
Vitexin	TRPV4 Antagonist	None reported	Mice	Experimental *in vivo* study	52
Cimifugin	TRPV4 Antagonist	None reported	Mice	Experimental *in vivo* study	53

5.2. TRPV1 Antagonists

The transient receptor potential vanilloid 1 (TRPV1) channel is a well-characterized mediator of pain, thermoregulation, and itch sensation, primarily expressed in sensory neurons and keratinocytes [37]. It is activated by heat, capsaicin, protons as well as pro-inflammatory mediators such as histamine, prostaglandins, and bradykinin, contributing to neurogenic inflammation and chronic pruritus. TRPV1 is rapidly desensitized, becoming unresponsive to further stimulation [38]. Given its role in itch transmission, TRPV1 antagonists have emerged as a promising therapeutic approach.

Asivatrep (PAC-14028), a selective TRPV1 antagonist, has demonstrated significant potential. In preclinical studies using rat and mouse models, a 1.0% cream formulation effectively suppressed AD-like skin inflammation [39]. It was later evaluated in a phase II clinical trial involving adult patients with mild to moderate

AD. Findings demonstrated that applying the 1.0% concentration cream twice daily for eight weeks led to fewer adverse events and improved symptoms such as inflammation and erythema [39]. More recently, a phase III trial evaluating Asivatrep's efficacy in adolescent AD patients showed significant improvement in clinical signs and symptoms with good tolerability [39] [40]. While further investigation of long-term safety is needed, Asivatrep holds excellent promise as a targeted therapy for neurocutaneous and chronic itch conditions by selectively antagonizing TRPV1.

However, not all TRPV1 antagonists have shown similar efficacy. SB705498, a 3% topical formulation, failed to demonstrate significant improvement compared to placebo [41] [42]. Notably, the 3% formulation was better tolerated and provided greater symptom relief than the 1% and 5% concentrations, suggesting that formulation and dosing strategies are critical for therapeutic success. These findings emphasize the need for continued exploration of TRPV1 antagonists with improved pharmacological properties for antipruritic treatment.

In addition to direct antagonists, modulators of TRPV1 have shown antipruritic effects. Topical acetaminophen has demonstrated a dose-dependent reduction of itch in healthy volunteers experiencing histamine-dependent and cowhage-induced pruritus, with no reported adverse effects such as skin irritation or discoloration [43]. Acetaminophen's metabolites are believed to act on TRPV1 receptors in C-fibers while also inhibiting inflammation through prostaglandin suppression [44]. However, the lack of data on its clinical use in patients with preexisting dermatological conditions limits its translation to chronic disease populations. Further research is needed to confirm its efficacy and safety in broader patient cohorts.

Topical cannabinoids also modulate TRPV1 receptors, influencing oxidative stress and immune responses. Cannabinoids have been explored for systemic conditions and cholestatic pruritus, with some evidence supporting their efficacy. For example, N-palmitoylethanolamine (PEA), a cannabinoid-like mediator, provided complete itch relief in 38% of participants with uremic pruritus in a non-randomized study of 21 individuals [38] [44]. Additionally, cannabinoids have been investigated in dermatological conditions such as AD, showing a 30% reduction in pruritus in a study of 14 patients [44]. While topical formulations are reportedly well tolerated, they may cause contact dermatitis, necessitating cautious use. Some over-the-counter moisturizers already contain topical cannabinoids, increasing accessibility for patients.

A major limitation of systemic TRPV1 antagonists has been the development of hyperthermia, most notably observed with AMG-517 in a suspended clinical trial [36]. The mechanisms underlying this effect are not fully understood, but several hypotheses have been proposed. One proposes that TRPV1 receptors expressed in the hypothalamic preoptic area, a region associated with thermoregulation undergo ligand-induced stimulation. Another mechanism is that TRPV1 receptors on vascular smooth muscle may alter vascular tone and affect heat loss.

Alternatively, given that TRPV1 channels can be activated by different stimuli such as capsaicin, heat and protons, inhibition of proton activation has been proposed to be associated with hyperthermia [45]. Finally, structural studies suggest that binding orientation is important with Huang *et al.* reporting that antagonists that interact closely with S4-S5 linker region of the receptor are more likely to cause hyperthermia than those that avoid this domain [46].

Overall, TRPV1 antagonists represent a promising avenue for pruritus management. Compounds like Asivatrep demonstrate significant clinical benefits, while the inconsistent efficacy of others such as SB705498, underscores the complexity of targeting this pathway. Emerging therapies, including topical acetaminophen and cannabinoids, offer alternative mechanisms for TRPV1 modulation, though their long-term efficacy and safety require further validation. With growing insight into how systemic TRPV1 antagonism induces hyperthermia, newer compounds that do not impair proton activation or avoid the S4-S5 linker domain, as well as topical approaches, may improve safety. Future research should focus on optimizing formulation, delivery methods, and patient selection to maximize the therapeutic potential of TRPV1-targeted treatments in chronic pruritus.

5.3. TRPA1 Antagonists

The transient receptor potential ankyrin 1 (TRPA1) channel is a key mediator of chronic pruritus, particularly in response to environmental irritants, mechanical stimuli, and oxidative stress. Expressed in sensory neurons and keratinocytes, TRPA1 contributes to neurogenic inflammation through histamine-independent pathways, making it an attractive target for conditions such as AD.

Preclinical studies have demonstrated TRPA1's role in mediating itch. In TRPA1 knockout mice with AD-like pruritus, scratching behavior was significantly reduced despite elevated thymic stromal lymphopoietin (TSLP), a key inflammatory mediator in AD [47]. Similarly, the TRPA1 antagonist HC-030031 (intraperitoneal 100 mg/kg) alleviated itch in transgenic mice overexpressing IL-13, a cytokine implicated in AD-associated inflammation [48]. Another study found that the TRPA1 antagonist A-967079 (topical 30 mg/kg) reduced scratching behavior in mice with tacrolimus-induced pruritus [49]. Since tacrolimus, a widely used topical calcineurin inhibitor for AD can induce pruritus, TRPA1 antagonists may serve as adjuvant therapies to mitigate this adverse effect. Despite promising preclinical evidence, no clinical trials currently investigate TRPA1 antagonists for dermatological pruritus in humans. However, existing topical treatments such as menthol and camphor, which have demonstrated antipruritic effects, may provide indirect TRPA1 inhibition.

Menthol, primarily known for its cooling effects via TRPM8 activation, also inhibits TRPA1, thereby contributing to itch relief [50]. A menthol derivative, menthoxypropanediol (MPD), improved pruritus in 95% of AD patients within 30 minutes of application, with 90% experiencing sustained relief for at least 15 minutes [44]. Similarly, camphor, which has been studied for prurigo nodularis

and contact dermatitis, inhibits TRPA1 at higher concentrations, leading to analgesic and antipruritic effects [44]. However, prolonged use of camphor can cause contact dermatitis. While TRPA1 antagonists remain in preclinical development, repurposing topical agents like menthol and camphor may provide immediate therapeutic benefits for pruritic conditions. Further clinical studies are needed to validate their efficacy in TRPA1-mediated itch disorders.

5.4. TRPV4 Modulators

TRPV4 is a mechanosensitive and thermosensitive TRP channel implicated in itch modulation. Unlike TRPV1 and TRPA1, TRPV4 is widely expressed in skin cells, including keratinocytes, macrophages, and sensory neurons, making it a potential target for pruritus treatment.

Emerging preclinical studies suggest that TRPV4 modulation may provide new therapeutic avenues. Crotamiton, a medication primarily used for scabies, has been investigated for its potential role in non-scabies-related itch by inhibiting TRPV4 in a dose-dependent manner [51]. In mice, 30 μL crotamiton oil alleviated scratching behavior induced by subcutaneous injection of a TRPV4 selective agonist [51]. While crotamiton's mechanism of action was previously unclear, its identification as a TRPV4 inhibitor supports the opportunity to repurpose it for TRPV4-mediated itch conditions. Similarly, Vitexin, a flavonoid compound with potent analgesic effects, has demonstrated antipruritic effects in both histamine-dependent and histamine-independent pruritus models at a dose of 7.5 mg/kg intravenously [52]. Although vitexin remains in the preclinical phase and is not yet used clinically, its anti-inflammatory, antioxidant and antipruritic properties justify further investigation in chronic itch conditions. Cimifugin, a component of traditional Chinese medicine, acts as a TRPV4 inhibitor and significantly reduces psoriatic pruritus in mice models when given intragastrically (75 mg/kg) [53]. Given that psoriatic patients experience diminished quality of life due to relapsing, treatment-resistant symptoms and also exhibit high TRPV4 expression in skin cells, repurposing cimifugin as a TRPV4-targeted therapy warrants further exploration.

While TRPV4-targeted therapies remain in early development, these findings suggest a promising role in pruritus management. Future studies should focus on refining TRPV4-targeted compounds to improve efficacy and safety in chronic itch treatment.

5.5. Targeting Downstream Pathways

Calcitonin gene-related peptide (CGRP) is released from sensory nerve terminals and plays a key role in vasodilation, inflammation, and the transmission of pain, itch, and noxious stimuli. Similarly, substance P is another neuropeptide involved in pain and itch. CGRP contributes to inflammation through neurogenic dilation of arterioles, while substance P increases the vascular permeability of venules [54]. In the context of pain and itch, CGRP and substance P are released in the skin

following protease-activated receptor 2 (PAR2) activation, leading to nerve sensitization [55]. PAR2, expressed in sensory neurons, mast cells, and keratinocytes, is activated by tissue injury and mediates histamine-independent itch [56]. Another key receptor in this pathway, TRPV1, is found on C- and Aδ-fibers and triggers the release of CGRP and substance P, further amplifying inflammation [57]. Notably, PAR2 has been shown to sensitize TRPV1 [58]. Thus, the interplay between these neuropeptides and receptors highlights the complex mechanisms that regulate pain, itch, and inflammation within neuro-immune signaling.

The release of CGRP and substance P amplifies inflammation and modulates sensory transmission. These neuropeptides act synergistically in key signaling pathways, where activation of receptors such as TRPV1 and PAR2 propagates pain and itch. In mouse models, Costa *et al.* demonstrated that trypsin-induced itching was significantly enhanced via PAR2 and TRPV1 receptor activation, with the subsequent release of CGRP and substance P mediating the itch sensation [57]. Selective antagonists of these receptors attenuated the response, underscoring their role in itch signaling [57]. Interventions such as the PAR2 antagonist FSLLRY, lima bean trypsin inhibitor, celecoxib, as well as TRPV1 blockade achieved through antagonism, gene editing, or C-fiber desensitization, all effectively reduced the itch response [57]. Furthermore, Rogoz *et al.* identified vesicular glutamate transporter 2 (VGLUT2) as a mediator of itch through TRPV1 and suggested additional potential targets, such as CGRP and the gastrin-releasing peptide receptor (GPCR) for itch modulation [59]. Akiyama *et al.* further proposed that neurokinin-1 (NK-1) antagonists, gastrin-releasing peptide (GRP) inhibitors, and AMPA receptor antagonists could represent therapeutic strategies for substance P-mediated chronic itch [60]. These findings highlight TRPV1, PAR2, and their downstream pathways as promising targets for therapeutic modulation of pain and itch.

5.6. Biologics and Cytokine Modulation

Cytokines such as IL-31, IL-4, and IL-13 are interleukins involved in inflammatory responses. IL-31 is primarily associated with conditions like AD and chronic itch, while IL-4 and IL-13 are key players in Th2 immune responses, particularly in allergic diseases. Targeting these interleukins has led to novel therapeutic approaches for cytokine-driven pruritus. Dupilumab, an IL-4 receptor antagonist was approved in 2017 for adults with moderate-to-severe AD not adequately controlled by topical therapy and remains a first line systemic agent, although newly approved alternatives are now available.

In moderate-to-severe AD adolescents and adults, the ARCADIA 1 and 2 phase III trials showed that Nemolizumab, an IL-31 receptor antagonist, in conjunction with topical therapy significantly improved pruritus and skin inflammation. Participants were given 30 mg (once every 4 weeks, with a 60 mg loading dose at baseline) subcutaneously of Nemolizumab with or without topical calcineurin inhibitors for 16 weeks, and had significant improvement in skin clearance, sleep,

and pruritus with Nemolizumab plus topical therapy [61]. Similarly, two phase III clinical trials, ADvocate1 and ADvocate 2, report 250 mg (given every 2 weeks with a 500 mg loading dose at baseline) subcutaneously of Lebrikizumab significantly improved skin clearance, itch and reduced sleep interference by 16 weeks [62]. These two therapies are now FDA-approved for the management of moderate-to-severe AD in individuals aged 12 years and older [63]. These targeted therapies represent a major advance in treatment of cytokine-driven chronic pruritus, offering improved outcomes for patients with recurrent skin conditions. By targeting the underlying cytokine pathways, these therapies hold the potential to provide long-term relief and reduce the burden of chronic pruritus.

These biologics, which target various interleukin and cytokine pathways, focus on immune mechanisms involved in chronic itch and modulate the immune response [64]. In contrast, TRP channel modulators target sensory pathways associated with chronic itch, such as TRPV1, which has been shown to interact with CGRP and substance P, as previously described. Modifying TRP channels reduces neuronal activation linked to the itch response [47]. Additionally, Mahmoud *et al.* suggest that IL-31 promotes TRPA1 transcription in atopic dermatitis and stimulates sensory neurons by interacting with receptors that lead to TRP channel activation [19]. Combining biologics with TRP channel modulators provides a multimodal approach to managing chronic itch. Biologics reduce inflammation and cytokine release, while TRP modulators attenuate itch sensory perception, offering disease-modifying and symptomatic relief. Addressing both immune and neuronal pathways enhances treatment efficacy in conditions characterized by immune dysregulation and increased neuronal activation.

6. Future Directions

The multifaceted nature of chronic itch presents significant challenges in research and clinical management. Limitations in preclinical murine models, variations in receptor expression between species, and the subjective nature of itch perception limit the ability to standardize symptoms and treatment. Similarly, there is ongoing debate regarding optimal delivery methods, including novel approaches to nanomaterials. Translation of *in vivo* murine data to human models remains uncertain, as receptor density and distribution differ significantly between species. Although Mas-related G protein coupled receptors (MRGPRs), TRP channels, serotonin receptors and IL-4/13/31 receptors have been identified in both mice and humans, their relative expression patterns remain incompletely defined and require further investigation [65].

Recent research highlights the interplay between itch-sensing TRP channels, cytokines, and the immune cells in perpetuating the itch-scratch cycle. While TRP channels are implicated in chronic itch, their precise roles in signal transduction and disease-specific pathways remain unclear [14]. Furthermore, TRP channels regulate other biological functions, such as pain transmission and temperature recognition [66]. Due to their various functions, concerns remain about unin-

tended side effects when targeting TRP channels therapeutically.

In addition to molecular mechanisms, delivery methods for chronic itch treatment pose challenges. Nanotechnology has emerged as a promising strategy for transdermal drug delivery, but concerns remain regarding the environmental impact of nanomaterials. Nanoparticles must penetrate the skin barrier through the lipid matrix, sweat glands (60 - 80 micrometers), or pilosebaceous pores (10 - 70 micrometers) to elicit its effects [67]. Similarly, they must be small enough to pass through the multiple layers of the dermis and the basement membrane to exert their therapeutic effects via systemic circulation. The efforts needed for nanoparticles to penetrate skin pose challenges in optimizing their size and composition for effective systemic absorption while concurrently mitigating environmental risks.

Ongoing research into the neuro-immune mechanisms of chronic itch provides new therapeutic avenues. Interleukin-4, IL-13, and IL-31 remain central targets, with emerging evidence implicating IL-33 in activating innate immune responses to itch [65]. IL-33 is released by keratinocytes, endothelial cells, and immune cells and may play a critical role in the itch-scratch cycle [68]. Once itch is detected by TRPV1, a TRP channel implicated in histaminergic itch, IL-33 is released and activates the innate immune system to stimulate the expression of IL-4 and IL-13 [16]. The downstream signaling of these cytokines induces the expression of IL-31, which produces itch. Although precise concentration-response relationships remain unclear, IL-33 is consistently overexpressed in chronic itch conditions such as atopic dermatitis and allergic contact dermatitis [65] [68]. Notably, several studies have found elevations in IL-33 levels in skin and blood of patients with AD with levels being correlated with clinical severity [69] [70].

Furthermore, knockout studies in murine models suggest that blocking IL_33 signaling may prevent chronic itch development independently of the action of immune cells [69]. The neuro-immune approach also provides insight into chronic itch conditions that lack inflammation, such as Chronic Idiopathic Pruritus, Nostalgic Paresthesia, and Scalp Pruritus [71]. In these cases, neuronal dysfunction rather than immune activation drives symptoms, highlighting the need for treatments targeting neural pathways. In a recent study on TRPA1, a TRP channel involved in non-histaminergic itch, found that knockout mice exhibited reduced itch secondary to IL-31 activation [19]. Focusing on combining biologics with TRP channels is promising, as it has the potential to address both the immune and neuronal components of itch and further exploration can lead to novel biologic therapies.

The complexities in chronic itch, influenced by genetic and environmental factors, underscore the need for continued research in both mechanistic and therapeutic domains. Advancing human clinical trials on TRP channel modulators and IL-4/13/31 inhibitors will be pivotal in developing effective treatments. Addressing the safety and side-effect profiles of TRP-targeting therapies remains a key challenge for their clinical implementation. Ultimately, personalized approaches

will be necessary to improve patient outcomes and can be further improved by developing innovative therapies that address neuro-immune mechanisms of chronic itch.

7. Conclusions

Chronic itch is a debilitating symptom of various dermatologic and systemic conditions, significantly impairing patients' quality of life. Recent research has highlighted intricate neuro-immune mechanisms underlying pruritus, particularly the role of transient receptor potential (TRP) channels such as TRPV1, TRPA1, and TRPV4 as important mediators in the pathogenesis of pruritus. These channels link immunological, environmental, and neuronal stimuli, modulating how itch signals are processed and perceived. Dysregulation of these pathways perpetuates the itch-scratch cycle, positioning TRP channels as important therapeutic targets.

As shown in Table 1, emerging therapies have targeted TRP channels and are aimed at combating the amplification of chronic itch. TRPV1 antagonists such as Asivastrep have demonstrated efficacy in both preclinical and phase III trials, although systemic agents such as AMG-517 were limited by hyperthermia, prompting the development of safer design strategies and topical formulations. For TRPA1, preclinical antagonists such as HC-030031 and A-967079 reduced scratching in models of AD and tacrolimus-induced itch, while topical agents like menthol, menthoxypropandediol, and camphor provide indirect TRPA1 inhibition and have shown rapid symptomatic relief in patients. TRPV4 modulators such as crotamiton, vitexin, and cimifugin, illustrate drug repurposing and the potential of natural compounds to target pruritic pathways. In parallel, biologic agents targeting IL-31, IL-4, and IL-13 have demonstrated efficacy in phase III trials, with Nemolizumab and Lebrikizumab now FDA-approved for moderate-to-severe AD. Together, these advances highlight how targeting immune and sensory pathways provides more comprehensive and durable relief.

Despite these advances, significant challenges remain before such discoveries can be translated into routine care. Current preclinical models do not fully capture the complexity of chronic itch in humans, limiting their predictive value. Long-term efficacy and safety data for many TRP modulators are lacking; optimal delivery methods remain an area of active investigation. Nanotechnology and advanced topical formulation offer potential solutions, but further research is required to optimize their safety, penetration and environmental sustainability.

Bridging these gaps is essential for developing personalized, long-lasting treatments for chronic itch. Given its complex and heterogeneous nature, future therapeutic strategies will likely benefit from multimodal approaches that integrate biologic, TRP channel modulators, and innovative delivery systems. Since chronic itch manifests across patients, individualized regimens will be key. Continued exploration of the molecular mechanisms underlying itch, coupled with advances in targeted therapy, holds promise for improving patient care and enhancing quality of life.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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