

Mechanisms of pruritus and advances in traditional Chinese medicine therapy (Review)

HAILING ZHANG^{1*}, YONGJI LI^{2*}, YUAN LIU¹, DANYI FENG¹, LETAO ZHAO¹,
RAN CHEN¹, XIWU ZHANG² and JINJIN DOU³

¹Graduate School, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150006, P.R. China;

²Research Institute of Chinese Medicine, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150006, P.R. China; ³Department of Cardiology, The Fourth Hospital of Heilongjiang University of Chinese Medicine,

Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150040, P.R. China

Received October 23, 2025; Accepted February 13, 2026

DOI: 10.3892/mmr.2026.13917

Abstract. Pruritus is a multifaceted and complicated symptom with an increasing global incidence as a result of increased environmental stressors and aging populations, making it a notable public health concern. Although research has investigated the multifaceted pathophysiological causes of pruritus, the entire range of pathophysiological processes is currently unknown. Furthermore, contemporary Western medicines continue to have drawbacks, including low efficacy and marked side effects. Traditional Chinese medicine (TCM), on the other hand, exhibits notable therapeutic potential in the treatment of pruritus due to its systemic regulatory benefits via multicomponent, multitarget and multichannel processes. The present review outlines the current understanding of the pathogenesis of pruritus and summarizes contemporary therapeutic approaches established in TCM, with a focus on summarizing the pharmacological effects and mechanisms of active constituents found in single-agent treatment herbal remedies and compound formulations. The aim of the present review is to provide a theoretical foundation and strategic advice for the development and clinical translation of novel TCM medications with extensive regulatory functions.

Contents

1. Introduction
2. Initiation, transduction, amplification and central integration of pruritus
3. TCM
4. Conclusion

1. Introduction

Pruritus is a warning abnormal sensation elicited by stimuli that frequently results in intense scratching impulses that markedly impair the sleep, mood and quality of life of patients (1), as well as potentially causing skin damage, secondary infections or even life-threatening complications (2-4), making it a key public health issue. Pruritus has a complex etiology, with clinical classification typically divided into four categories (5-7): i) Cutaneous (derived from skin diseases such as allergic, inflammatory or infectious conditions, as well as insect bites); ii) systemic (extracutaneous diseases such as hepatic, renal, hematological or drug-related disorders); iii) neuropathic (secondary to neurological diseases); and iv) psychogenic (conditions directly triggered by psychosocial factors are closely associated with neuropsychiatric disorders, such as anxiety disorders, depressive disorders and somatic symptom disorders). These categories frequently coexist, resulting in mixed pruritus, which is more common [in the etiological classification of chronic pruritus, mixed etiology (e.g., coexistence of inflammatory and neuropathic factors) is a critical consideration] in clinical practice (8). For example, elderly individuals are more likely to develop mixed pruritus due to factors such as decreased sebum secretion and natural degradation of their skin barrier (9), as well as multiple chronic comorbidities (systemic) and neurodegenerative changes (neuropathic), making them a particularly high-risk group. Furthermore, environmental factors such as pollution weaken the skin barrier, raising the global risk of pruritus-related disorders in ~3 billion individuals (10), highlighting the complexity and urgency of prevention and therapy.

Correspondence to: Professor Jinjin Dou, Department of Cardiology, The Fourth Hospital of Heilongjiang University of Chinese Medicine, Heilongjiang University of Chinese Medicine, 24 Heping Road, Xiangfang, Harbin, Heilongjiang 150040, P.R. China
E-mail: doujinjin1980@126.com

Professor Xiwu Zhang, Research Institute of Chinese Medicine, Heilongjiang University of Chinese Medicine, 24 Heping Road, Xiangfang, Harbin, Heilongjiang 150006, P.R. China
E-mail: 149772105@qq.com

*Contributed equally

Key words: pruritus, pathogenesis, traditional Chinese medicine therapy, active components, compound formulations

A deeper understanding of pruritus processes is therefore necessary for developing novel therapies. According to a previous study (11), pruritogens stimulate sensory nerve terminals through damaged epidermal barriers or immune cell activation, stimulating a number of receptors [examples include G protein-coupled receptors (GPCRs) such as protease-activated receptors 1/2 (PAR-1/2), Mas-related G protein-coupled receptor (MRGPR) subtypes (e.g., MRGPRD, MRGPRX1, MRGPRX2), serotonin (5-HT) receptors including 5-HTR2B, and cytokine receptors such as interleukin-31 receptor A (IL-31RA) mediating IL-31 signaling, and IL-17 receptor A (IL-17RA) binding IL-17A] and changing transient receptor potential (TRP) as well as voltage-gated sodium (NaV) channels to generate action potentials. These signals are subsequently transmitted to regions in the brain such as the parabrachial nucleus (PBN) and amygdala through spinal gastrin-releasing peptide receptor (GRPR) neurons, whereby affective and motivational states are modulated, ultimately resulting in the 'pruritus-scratch' cycle.

Currently, Western medicine treats symptoms primarily with antihistamines, glucocorticoids and immunomodulators, which exhibit short-term efficacy but are associated with long-term risks, such as skin atrophy (12), pigmentation, increased infection susceptibility (13) and relapse after discontinuation, limiting long-term relief (14). Traditional Chinese medicine (TCM) has been used in the treatment of pruritus for a long time, with emphasis on syndrome differentiation and general regulation. TCM therapy has shown a unique ability to alleviate symptoms, reduce recurrence and improve quality of life (15) by integrating synergistic multi-component, multi-target and multi-pathway effects of single herbal active components and compound formulations (16). However, despite its promising efficacy and safety, the precise mechanisms of TCM treatment and the complex interactions between its components are unclear (15,16), hindering the development and practical application of novel TCM therapies. To address this, in the present review, a novel mechanistic framework for pruritus that includes the sequential phases of 'initiation-transduction-amplification-central integration' was developed, methodically clarifying the pathogenic underpinnings. Furthermore, the present review describes TCM intervention strategies at the molecular level, demonstrating that active compounds from single herbs and conventional compound formulations work together to modulate pruritus signaling networks through multi-target interactions. In addition, the present review explores multidimensional and multilevel action pathways, as well as advancements from single herbs to compound formulations, effectively bridging the gap between the theoretical framework of TCM and the modern pathophysiological mechanisms of pruritus, unlike existing studies that focus on monolithic Western medical perspectives (17) and related guidelines emphasizing clinical workflows over mechanistic explanations (18). The aim was not only to deepen the systemic understanding of pruritus pathogenesis but also to provide a robust theoretical foundation for novel drug development, clinical precision translation and innovative integrative TCM-Western medicine therapeutic strategies.

2. Initiation, transduction, amplification and central integration of pruritus

Initiation: Pruritogen recognition and signal perception. Skin pruritus is caused by both histamine and non-histamine mechanisms (19). Keratinocytes create pruritogens locally, which move to the skin through the circulation pathway and activate sensory nerve endings (20). The peripheral nerves are classified into three types: i) A β fibers (myelinated and mechanosensitive); ii) A δ fibers (thinly myelinated); and iii) C fibers (unmyelinated) (11). Itch signals are primarily transmitted by A δ /C fibers (11). The histamine system employs histamine receptors, whereas the non-histamine pathway is activated by a number of pruritogens that target specific receptors (21). These two pathways join, using Mas-related G protein-coupled receptor (MRGPR) signaling to construct a dual regulatory network (22) (Fig. 1). Pruritus-related biochemical receptors interact with G protein-coupled receptors (GPCRs; main subtypes) or the Janus kinase (JAK)/STAT pathway (cytokine/chemokine receptors) to activate TRP and NaV channels, resulting in action potentials (11). These impulses are then transmitted to the spinal cord through ascending channels to the brain (23), causing the sensation of pruritus (Fig. 2).

MRGPRs. MRGPRs are primary regulators of non-histamine-dependent pruritus, with pruritogens activating a number of pathways [Gq protein-coupled signaling cascades (24), Gi protein signaling pathways (25), calcium mobilization and calcium-dependent pathways (26,27) and TRP ion channel signaling routes (28)] (Fig. 3). The rodent MRGPRA/B/C and primate MRGPRX subfamilies are particularly important in this area of pruritus research (29).

Chloroquine (CQ) treatment in patients with malaria in Africa frequently causes intense pruritus (30). A study showed that mice lacking a cluster of 12 MRGPR genes exhibit reduced scratching after CQ administration, indicating that MRGPR-expressing neurons contribute to itch perception (31). CQ directly activates MRGPRA3, and ablation of MRGPRA3-expressing neurons [which constitute 5-8% of dorsal root ganglion (DRG) neurons] alleviates both acute and chronic itch symptoms (31). These findings have established MRGPRA3 as a specific marker for neuronal pentraxin 2-positive pruriceptive neurons.

Bovine adrenal medulla (BAM)-8-22 and γ 2-melanocyte stimulation hormone can activate human MRGPRX1 and mouse MRGPC11, which are orthologous receptors (32,33). BAM8-22 is a strong agonist for both. Furthermore, activation of MRGPC11/X1 elicits varying effects depending on the site of action. Namely, subcutaneous activation of cutaneous sensory fibers causes itching (31), whereas intrathecal activation causes analgesia (34,35). As a result, an improved understanding of the functional roles of MRGPC11/X1 is required to create targeted therapeutic strategies for pain- and itch-related diseases.

MRGPRD is expressed in small-diameter DRG and trigeminal ganglion neurons (36). Its positive fibers are non-peptidergic, unmyelinated, mechanosensitive C-fibers that densely innervate the skin (37). β -alanine is a natural ligand for MRGPRD (38) in both humans and mice and directly activates this receptor, inducing itch in numerous

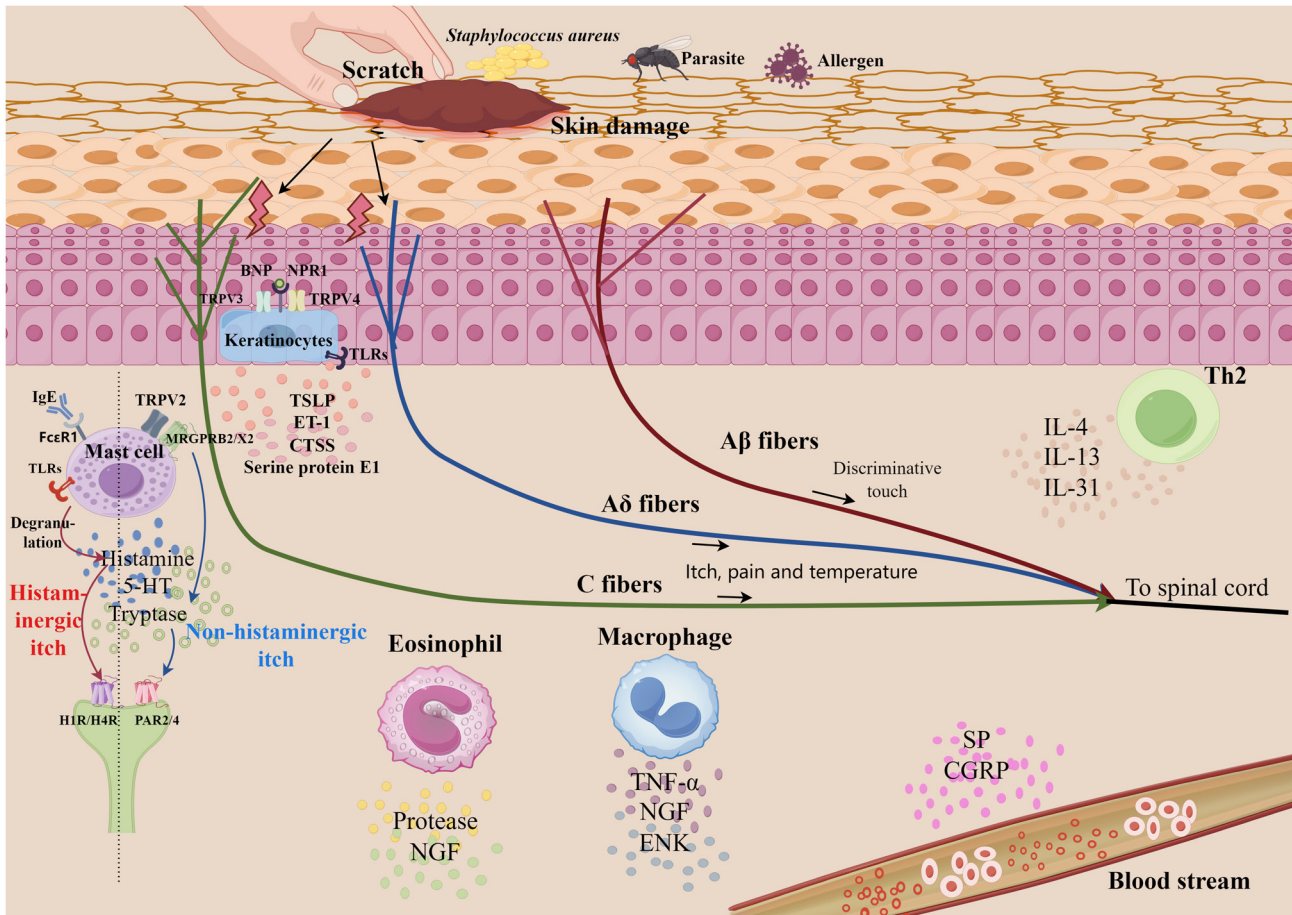


Figure 1. Transmission process of pruritus in the skin. Histaminergic and non-histaminergic itch pathways. FcεR1, Fc ε receptor 1; MRGPRB2/X2, mas-related G protein coupled receptor-B2/X2; TLR, toll-like receptor; TRPV, transient receptor potential vanilloid; 5-HT, 5-hydroxytryptamine; H1/4R, histamine receptor type 1 and 4; PAR, protease-activated receptor; BNP, brain natriuretic peptide; TSLP, thymic stromal lymphopoietin; ET-1, endothelin 1; CTSS, cathepsin S; NGF, nerve growth factor; ENK, enkephalin; SP, substance P; CGRP, calcitonin gene-related peptide; NPR1, natriuretic peptide receptor 1; Th2, T-helper 2 cell.

individuals. Neurons from MRGPRD-knockout mice exhibit no response to β-alanine (39). In addition, in a model of atopic dermatitis (AD), the excitability of MRGPRD⁺ neurons was increased (40), suggesting a role for MRGPRD in both acute and chronic itch (41).

MRGPRB2 and its human ortholog MRGPRX2 are specifically expressed in connective tissue mast cells and may be activated by exogenous drugs or endogenous neuropeptides such as substance P (SP) (42,43). Activation of MRGPRB2 primarily triggers mast cell release of tryptase, which in turn drives non-histaminergic itch pathways (44-46). MRGPRX2 expression is upregulated in patients with AD, psoriasis, allergic contact dermatitis and chronic urticaria (47). In disease models, MRGPRB2-deficient mice exhibited markedly reduced itch and inflammation symptoms (48,49), highlighting MRGPRX2 as a promising therapeutic target for allergic pruritus.

Elevated bile acid levels in the serum of patients with cholestatic disorders are associated with non-histaminergic pruritus (50). Bile acids can directly activate MRGPRX4 at physiological concentrations (51). Genetic deletion of its murine ortholog, MRGPRA1, markedly reduces scratching behavior in mice (52), whereas transgenic mice expressing human MRGPRX4 exhibit exacerbated scratching in both acute and chronic cholestasis models (53). These findings

indicate that MRGPRX4 is a potential therapeutic target for alleviating cholestasis-associated itch.

Protease-activated receptors (PARs). PARs act as a regulatory center, combining protease signaling and epidermal barrier failure. Kallikreins and mast cell-derived tryptase activate PAR2 and 4, resulting in pruritus. Mast cell tryptase stimulates PAR2 through the phospholipase C-β/inositol trisphosphate pathway, leading to IL-31 release and keratinocyte production of thymic stromal lymphopoietin (TSLP). This signaling cascade decreases filaggrin production through the ERK/JNK/MAPK pathway. PAR2 activation further causes mast cell degranulation, which releases cytokines that directly activate nerve terminals, resulting in a self-amplifying pruritic cycle (44,54,55). In an animal study, administration of the PAR2 inhibitor PA-235 has been shown to markedly reduce pruritic behaviors. Single-cell sequencing results continue to show that PAR2 expression levels in patients with AD lesional skin are positively associated with ‘SCORing Atopic Dermatitis’ scores (56,57). Furthermore, *Staphylococcus aureus* serine protease V8 directly activates PAR1 on sensory neurons, causing bacterial infection-induced itching (58).

Toll-like receptors (TLRs). Upon TLR detection of molecular patterns associated with infection or damage, inflammatory signaling through the myeloid differentiation

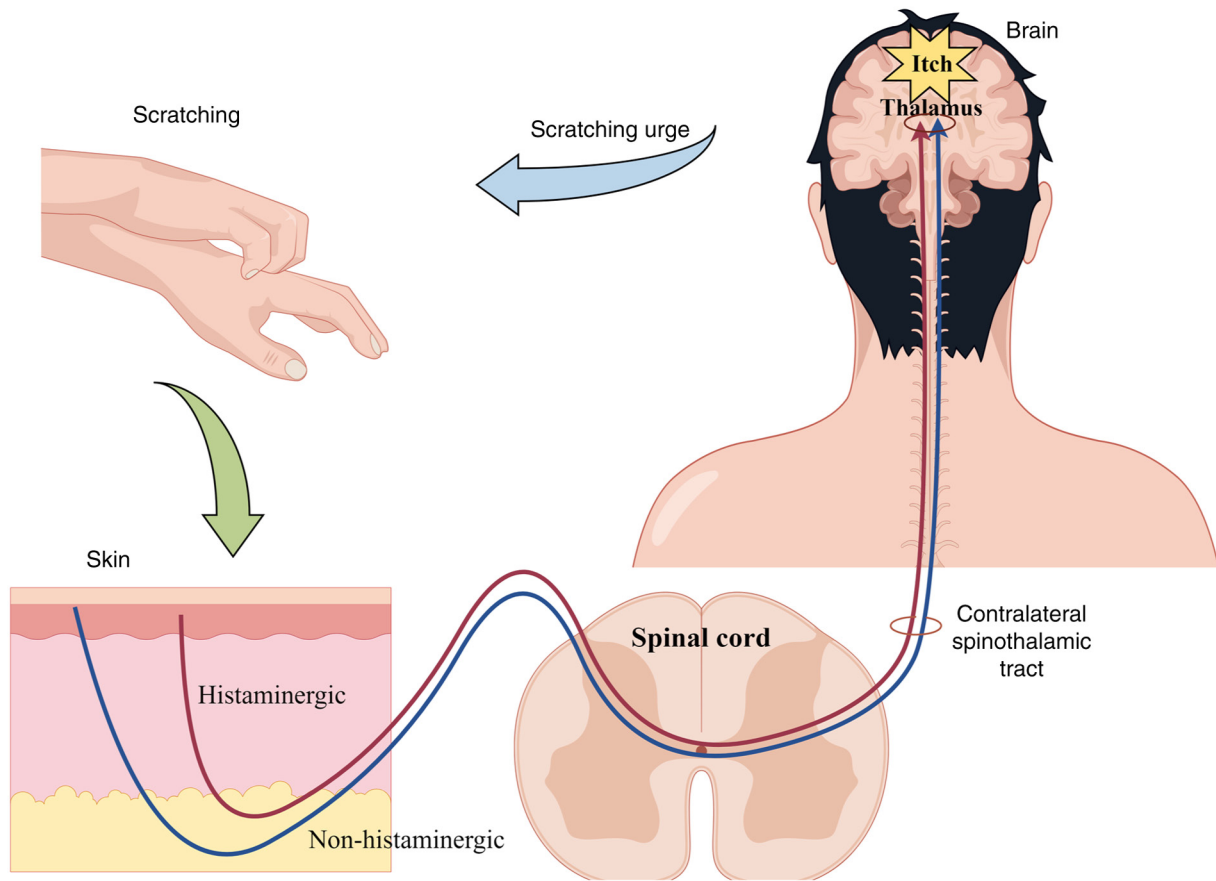


Figure 2. Transmission of prurceptive signals from the skin to the spinal cord and central nervous system.

primary response 88 (MyD88)/IL-1 receptor-associated kinase (IRAK)/TNF receptor-associated factor 6 (TRAF6) axis is activated. This activates the IKK complex, transports NF- κ B to the nucleus and promotes pro-inflammatory gene transcription (59,60). Activation of the MAPK (ERK/p38/JNK) pathway further initiates the production of cytokines (TNF- α , IL-1/6/12, IL-8 and macrophage inflammatory protein-2) as well as reactive oxygen/nitrogen species (61-63). These mediators are produced by immune cells and astrocytes, inducing local neuroinflammation and the transmission of pruritic signals (64,65) (Fig. 3).

DRG neurons that express TLR3/TRPV1 drive both histaminergic and non-histaminergic acute itching (66), as evidenced by agonist-induced scratching behavior in mice. Notably, isothiocyanates (including phenethyl isothiocyanate and sulforaphane) markedly reduce poly(I:C)/CQ-induced acute itch and oxazolone-induced chronic itch via inhibition of the TLR3 pathway (67).

TLR4 is located in the DRG, trigeminal ganglia and spinal glia (68), regulating both acute and chronic pruritus. TLR4 markedly improves histamine-dependent signaling in acute itch by raising TRPV1 activity but has little effect on CQ- or compound 48/80-induced reactions (69). Chronic stressors, such as dry skin, activate TLR4 in spinal astrocytes via the STAT3/lipocalin 2 axis (70,71); however, intrathecal TLR4 suppression markedly diminishes these responses (70,71). Psoriasis-associated human β defensin-2 activates cutaneous macrophage TLR4 (72), resulting in

inflammatory itch, whereas TLR4 inhibition reduces neurosensitization and T helper 2 (Th2)/innate immune factor release (73).

TLR5, unlike other TLRs expressed in small-diameter neurons, is predominantly expressed in medium-to-large DRG neurons (74) corresponding to A β -LTMRs, which mediate mechanical pruritus through activation of spinal urocortin 3-positive interneurons (75).

TLR7, which is expressed in DRG neurons with TRP ankyrin (TRPA)-1, is a key regulator of histamine-independent itch (76-78). Ligands such as imiquimod directly activate DRG neurons, causing scratching behavior and mediating chronic itch through TRPA1-dependent processes (79). Let-7b, a secreted extracellular microRNA, acts as an endogenous TLR7 ligand, contributing to pruriceptive signaling (80). TLR2 and TLR7 on epidermal keratinocytes promote the release of chemokine C-X-C motif ligand-1/2, IL-31, IL-33, IL-17A and TNF- α , which contribute to chronic itching in dry skin and psoriasis (81). Let-7b inhibits psoriatic epidermal differentiation by downregulating IL-6 and inhibiting ERK1/2 (82).

Transduction: Pruritus signaling pathway

TRP channels. TRP superfamily ion channels serve as key components in the regulatory network that coordinates the dynamic balance between neuronal activation and epidermal barrier homeostasis in the pathogenesis of cutaneous pruritus (83,84) (Fig. 3). The TRP superfamily ion channels are key downstream effectors of GPCRs and PARs (11,83).

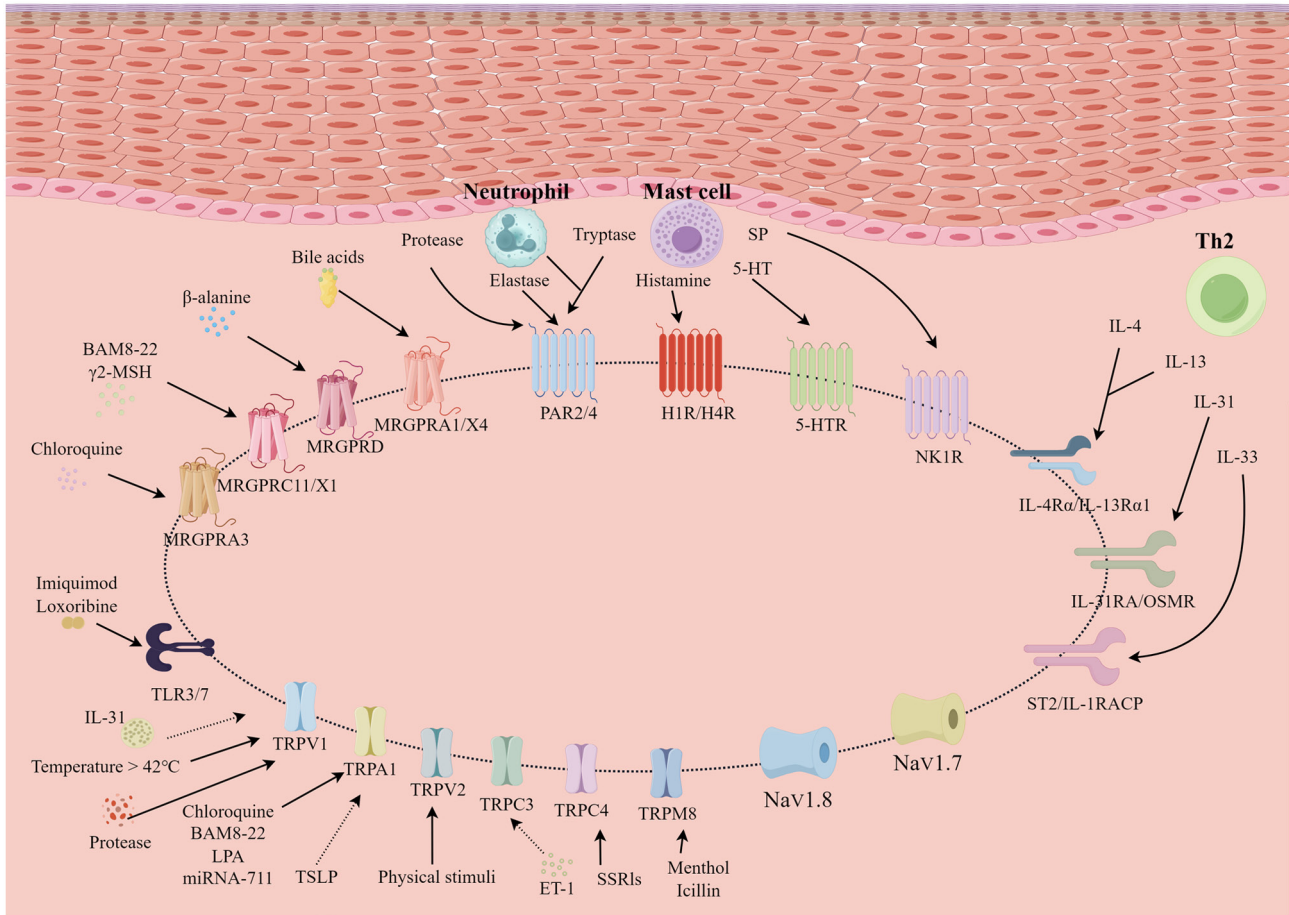


Figure 3. Receptors and ion channels involved in pruritus. Under conditions of cutaneous disorders or pruritogen exposure, these receptors and ion channels exhibit activation and mediate key functions in the pathogenesis of pruritus. BAM, bovine adrenal medulla; SP, substance P; 5-HT, 5-hydroxytryptamine; Th2, T-helper 2 cell; MRGPR, MAS-related G protein-coupled receptor; PAR, protease-activated receptor; TRPV, transient receptor potential vanilloid; TRPC, transient receptor potential canonical; SSRIs, selective serotonin reuptake inhibitors; TLR, toll-like receptor; TRPM8, transient receptor potential melastatin 8; TSLP, thymic stromal lymphopoietin; miRNA, microRNA; ET-1, endothelin 1; NaV, voltage-gated sodium; H1/4R, histamine receptor type 1 and 4; ST2, growth stimulation expressed gene 2; γ 2-MSH, γ 2-melanocyte stimulation hormone; TRPA1, transient receptor potential ankyrin 1; RACP, receptor accessory protein; 5-HTR, 5-hydroxytryptamine; NK1R, neurokinin 1 receptor; OSMR, oncostatin M receptor; $R\alpha 1$, receptor $\alpha 1$; RA, receptor A; LPA, lysophosphatidic acid.

The capsaicin receptor TRPV1 can detect high temperatures (>42°C), low pH (<5.9) and capsaicin. It is widely distributed throughout the skin and aids in the maintenance of the epidermal barrier, activating sensory neurons by binding to histamine receptors. PAR2 and PAR4 mediate non-histaminergic pruritus and contribute to chronic neuroinflammation by sensitizing TRPV1, thereby promoting pruritic responses (85).

Conversely, TRPA1 is a receptor for pain and itch, triggered by cold temperatures (<17°C), menthol or cinnamaldehyde. TRPA1 activity is regulated positively by numerous pruritus-associated GPCRs (86). TRPA1-knockout mice display markedly reduced acute scratching reactions to CQ, adrenomedullin and sphingosine-1-phosphate (87,88), as well as reduced scratching activity in chronic dry skin-induced itch paradigms (89).

Loss-of-function mutations in TRPV3 impair PAR2 activity in keratinocytes and reduce neuronal activation (90,91). By contrast, gain-of-function variants of TRPV3 are associated with AD and Olmsted syndrome, with pharmacological inhibition of TRPV3 alleviating atopic itch (85,92). Further studies have shown that IL-31 enhances TRPV3 expression in

keratinocytes through the natriuretic peptide receptor (NPR)-1 receptor in a brain natriuretic peptide (BNP)-dependent manner (IL-31 stimulates sensory neurons to release BNP, which then upregulates NPR1-mediated TRPV3 expression). This cascade promotes the release of serine protease E1 and facilitates itch signaling (93,94).

TRPV4 sends itch signals through Ca^{2+} influx and ERK phosphorylation, serving a role in 5-hydroxytryptamine (5-HT)-induced itching, as well as the accumulation of inflammatory mediators (95).

TRP melastatin (TRPM)-8 is a cold-sensitive ion channel that operates within the temperature range of 8-28°C (96,97). TRPM8 can be triggered by methoxypropanediol to reduce irritation and improve skin barrier restoration. TRPM8 optogenetic activation inhibits SP release from neurons in the spinal dorsal horn that express GRPR, disrupting the itch-scratch cycle (98).

TRP canonical (TRPC)-3 and TRPC4 are extensively expressed in primary sensory neurons and have been associated with pro-inflammatory sensitization (99). Mice that lack TRPC3/C4 exhibit markedly reduced scratching reactions

to non-histaminergic pruritogens (99). In a contact hypersensitivity model, TRPC3 expression and function in the trigeminal ganglia were both increased (99). TRPC3 inhibition, either pharmacological or genetic, reduces spontaneous scratching (99). Additional research has revealed that genetic deletion of TRPC4 notably reduced itching caused by the selective serotonin reuptake inhibitor medicine sertraline (100,101).

NaV channels. NaV channels control the intensity and duration of itch signals by altering the action potential threshold (102,103): Higher NaV channel activity increases neuronal excitability by lowering the action potential threshold, resulting in more frequent action potentials and enhanced pruritic signal intensity. The inactivation kinetics of NaV channels determine the duration of action potentials: slower inactivation prolongs action potential duration, sustaining pruritic signals, whereas faster inactivation shortens action potentials, leading to transient pruritic signaling. A study employing sodium channel-specific knockout mouse models (104) have shown that NaV1.7 and NaV1.9 are primarily involved in acute pruritic signaling, while NaV1.8 is associated with persistent itch pathogenesis. Additional research (105) has revealed that DA-0218, a computationally developed high-selectivity NaV1.7 inhibitor, reduced both nociception and pruritus in animal models. This drug exhibited broad-spectrum efficacy in inflammatory pain and lymphoma-induced persistent pruritus, indicating that NaV1.7 may be a suitable target for cross-disease pruritus treatment.

Amplification: Pruritus signal mediators

Biogenic amines. Spatiotemporal specificity of pruritic signaling is controlled by the biogenic amine system through a network of numerous receptor subtypes, including histamine and 5-HT (106). Histamine, a classical pruritogenic mediator, is primarily stored in mast cells and basophils, but keratinocytes produce trace amounts when disturbed (107). Histamine produced through IgE-Fc ϵ receptor I cross-linking or non-IgE mechanisms (such as neuropeptides or thrombin) activates TRPV1/TRPA1 channels through histamine receptor 1 (H1R)/H4R receptors (11), causing membrane depolarization through the phospholipase C/12-lipoxygenase pathway. This depolarization causes NaV1.7/NaV1.8-mediated action potentials in the DRG, as well as neuropeptide release, resulting in neurogenic inflammation and itching (11). In animal models (108), combined H1R/H4R blockade has been shown to reduce scratching more effectively compared with single-target inhibition, indicating that multi-receptor methods hold therapeutic promise. Furthermore, H4R promotes Th2 cell IL-5/IL-13 secretion, which accelerates the progression of AD (109), suggesting that blocking H4R could be a novel therapeutic option for AD.

5-HT regulates acute and chronic pruritus through a number of mechanisms using unique peripheral receptor subtypes as detailed in Table I (23,83,110-114), representing novel developments in individualized chronic pruritus treatment: Higher NaV channel activity increases neuronal excitability by lowering the action potential threshold, resulting in more frequent action potentials and enhanced pruritic signal intensity. The inactivation kinetics of NaV channels determine the duration of action potentials: Slower inactivation prolongs action potential duration, sustaining pruritic signals, whereas

faster inactivation shortens action potentials, leading to transient pruritic signaling (83).

Neuropeptides. Neuropeptides serve an important role in regulating the homeostasis of the 'neural-immune-cutaneous' interaction network (Table II). SP activates the mast cell surface receptors neurokinin 1 and MRGPRX2 (115,116), causing the production of inflammatory mediators such as histamine and tryptase (117,118), resulting in a cycle of neurogenic inflammation and pruritus (16). Calcitonin gene-related peptide (CGRP), which acts as an immunological modulator in AD, stimulates IL-13 production (119). Conversely, fluctuations in IL-13 levels reciprocally influence CGRP release and neuronal sensitization (16). IL-31 activates its receptor IL-31RA to trigger CGRP secretion, while CGRP subsequently suppresses CD4⁺ T cell proliferation and reduces IL-13 generation, establishing an 'IL-31→CGRP→IL-13' negative feedback axis. This axis dynamically modulates type 2 inflammatory intensity and pruritic manifestations (120), with CGRP levels adjusting downstream inflammatory outputs in response to upstream signals, implying a dynamic relationship with pruritus intensity. BNP, a pruritogenic neuropeptide, exhibits increased synthesis and release mediated by IL-31 in the skin tissues and *in vitro* models of nodular prurigo as well as the inflammatory microenvironment of AD. BNP levels are markedly raised in the lesional skin of patients with AD, where it activates the NPR1 receptor on keratinocytes (121), promoting periostin release and creating a positive feedback loop through the 'BNP-periostin' axis. Endothelin (ET)-1 promotes pruritus signaling through the ET-A and ET-B receptor-mediated pathways (122).

Cytokines. Th2 inflammatory axes establish a pruritic signaling amplification system by modulating the 'neural-immune-epidermal' interactive network (Table III; Fig. 3). The IL-4/IL-13 axis serves a central role in cutaneous inflammation and pruritus (123-126). IL-31, a pro-inflammatory cytokine secreted by Th2 cells, is a key driver of chronic pruritus when upregulated (127-131). IL-33, a dual-function protein from the IL-1 family, acts as a cytokine binding to the IL-1 receptor-like 1 (ST2) receptor on Th2 cells to regulate IL-17A and IL-31 production as well as induce mast cell degranulation (132). As a nuclear transcriptional regulator, IL-33 interacts with the NF- κ B p65 subunit in endothelial cells to facilitate inflammatory response progression (133-136). The IL-23/IL-17 axis is primarily implicated in the pathogenesis of psoriasis, AD and lupus erythematosus (137-139). TSLP serves a pivotal role in amplifying pruritic signaling in inflammatory skin diseases such as AD by activating dendritic cells to drive Th2-type immune responses (140-145).

Periostin and neurotrophic factors. The expression levels of periostin, an extracellular matrix protein expressed by keratinocytes and fibroblasts, are associated with the pathological course of pruritus (146-148). Concurrently, neurotrophic factors, including nerve growth factor and brain-derived neurotrophic factor, serve a role in pruritic and inflammatory pathologies through distinct neuroimmunomodulatory mechanisms, with a focus on the coordinated regulation of neuronal activation and immune cell chemotaxis, collectively forming a molecular foundation for neurogenic inflammation (149-153) (Table IV).

Opioids. Endogenous opioids, including β -endorphin and dynorphin A, affect pruritus through GPCRs, specifically the μ -opioid receptor (MOR) and κ -opioid receptor (KOR). MOR is

Table I. Functional mechanisms of 5-HT in pruritus.

Designation	Subtype	G protein type	Signaling pathway	Mechanism of action	(Refs.)
5-HT ₁	5-HT _{1A}	G _{i/o}	G _{i/o} inhibits AC and interacts with GRP-GRPR	Enhances the excitability of spinal dorsal horn neurons	(110)
	5-HT _{1F}	G _{i/o}	G _i -G _{βγ} activates PLCβ3 and further activates TRP channels	Peripheral sensory neuron calcium response	(111)
5-HT ₂	5-HT _{2A}	G _{αq/α11}	G _i -G _{βγ} activates PLCβ3 and further activates TRP channels	Glucose-sensing enhances TRPV4 function	(23,83)
	5-HT _{2B}	G _{q/11}	G _{q/11} -PLCβ3 activates TRPC4	Activates TRPC4 channels	(23,83)
5-HT ₃	-	Ion channel	Na ⁺ /K ⁺ channel activation induces calcium influx	Platelets release 5-HT, with enhanced temperature sensitivity	(83,112)
5-HT _{4/5/6}	-	G _s	G _s activates AC, further increasing cAMP levels	Not clearly defined, may be involved in chloroquine-induced pruritus and chronic xerosis models	(113,114)
5-HT ₇	-	G _s	G _{βγ} -AC promotes TRPA1 activation	Coupling with TRPA1 results in upregulation of spinal neuronal excitation	(83)

5-HT, 5-hydroxytryptamine; TRPV, transient receptor potential vanilloid; TRPC, transient receptor potential canonical; TRPA, transient receptor potential ankyrin; AC, adenylyl cyclase; GRP, gastrin-releasing peptide; GRPR, GRP receptor; PLCβ3, phospholipase C β-3; TRP, transient receptor potential.

Table II. Functional mechanisms of neuropeptides in pruritus.

Designation	Receptor	Mechanism of action	Functional role	(Refs.)
SP	NK1 and MRGPRX2	Activation of NK1 and MRGPRX2 receptors, triggering TRPV1 channel opening and physiological alterations at sodium/calcium sites	Promotion of neurogenic inflammation and induction of mast cell degranulation, releasing histamine and tryptase	(117,118)
CGRP	CGRPα/β	Modulation of immune cell function through CGRP receptors, enhancing IL-13 generation	Modulation of immune responses and involvement in epidermal barrier dysregulation	(119,120)
BNP	NPR1	Activation through the NPR1 receptor enhances TRPV3 channel-mediated release of serpine E1	Involvement in the pathological processes of AD and positive association with pruritus severity	(121)
ET-1	ET-A/ET-B	Activation through ET-A and ET-B receptors, forming a positive feedback loop with IL-25 to promote inflammatory responses	Exacerbation of pruritus and inflammatory responses in psoriasis and prurigo nodularis	(122)

SP, substance P; CGRP, calcitonin gene-related peptide; BNP, brain natriuretic peptide; ET, endothelin; NK1, neurokinin 1; MRGPR, Mas-related G protein-coupled receptor; NPR1, natriuretic peptide receptor 1; TRPV, transient receptor potential vanilloid; AD, atopic dermatitis.

highly expressed in inhibitory interneurons of the spinal dorsal horn, such as NPY⁺ or Vgat⁺ neurons. β-endorphin, an endogenous MOR agonist, inhibits the activity of these inhibitory neurons upon MOR activation, thereby lifting their suppression on gastrin-releasing peptide (GRP)-positive pruriceptive neurons (i.e., ‘disinhibition’). This disinhibition hyperactivates the

GRP-GRPR microcircuit, amplifying pruritic signal transmission to the brainstem (154,155). Specific knockout of the *Oprm1* gene in NPY or Vgat⁺ neurons completely abolishes morphine-induced pruritus, confirming the central role of this pathway (154,155). Under pathological conditions such as atopic dermatitis, MOR activation upregulates pruritic mediators (e.g., IL-31) and

Table III. Functional mechanisms of cytokines in pruritus.

Designation	Source	Receptor	Mechanism of action	Function	(Refs.)
IL-4/IL-13	Th2 cells, eosinophils, basophils and mast cells	Shared receptors IL-4R α /IL-13R α 1 (functional receptor) and decoy receptors IL-13R α 2 (specific to IL-13)	Regulation of gene expression through the JAK/STAT signaling pathway, inhibiting the expression of keratinocyte differentiation proteins (such as filaggrin and keratin)	Co-potential of Th2 inflammatory responses, upregulation of alarmins such as TSLP, IL-25 and IL-33, as well as disruption of epidermal barrier function	(123-126)
IL-31	Th2 cells and granulocytes	IL-31RA/OSMR β (heterodimer)	Activation of JAK/STAT, PI3K/AKT and MAPK signaling pathways, inducing a delayed pruritic response	Directly activates sensory neurons to elicit pruritus and modulates keratinocyte function, perpetuating inflammatory cycles	(127-131)
IL-33	Keratinocytes, epithelial cells, dendritic cells, mast cells and fibroblasts	ST2 receptor (forms a heterodimer with IL-1R1)	Functions as an epithelial alarmin, activating Th2 cells to secrete IL-17A and IL-25, and regulates inflammatory responses through NF- κ B-mediated signaling	Triggers cutaneous TH2 responses, downregulates barrier proteins such as tight junction proteins (e.g., Claudin-1), and promotes neurogenic inflammation.	(132-136)
IL-23/IL-17	Dendritic cells, macrophages and Th17 cells	IL-17R	Augments neuronal sensitivity	Elevation of plasma IL-17 levels	(137-139)
TSLP	Keratinocytes, dendritic cells, mast cells and fibroblasts	TSLPR/IL-7R α (heterodimer)	Induces pruritus-associated gene expression through the JAK1/JAK2/STAT5 signaling pathway and facilitates dendritic cell migration and Th2 responses	Induces pruritus and inflammation, promotes dendritic cell migration and Th2 responses, and upregulates IL-33 expression	(140-145)

TSLP, thymic stromal lymphopoietin; Th, T helper; R α , receptor α ; RA, receptor A; OSMR β , oncostatin-M receptor- β ; ST2, IL-1 receptor-like 1; JAK, Janus kinase; R1, receptor type 1; TSLPR, TSLP receptor.

enhances TRP channel activity, intensifying peripheral neuronal sensitization and exacerbating itch perception (156). KOR agonists (e.g., nalfurafine) selectively suppress spinal efferent neurons expressing GRPR projecting to the lateral parabrachial nucleus/lateral spinal nucleus, blocking the transmission of pruritic signals to higher brain centers (157). Activation of the β -endorphin-MOR axis causes pruritus, while dynorphin A-KOR signaling reduces symptoms, creating functionally opposing roles. An imbalance in ligand binding to MOR and KOR in both plasma and the epidermis may exacerbate pruritus in individuals with psoriasis, Alzheimer's disease or liver disease (158-163).

Central integration of pruritus

Spinal dorsal horn signal integration. Spinal pruriceptive signaling requires a dynamic balance between excitatory and

inhibitory circuits. GRP-expressing neurons in the spinal cord use GRP receptors to relay peripheral itch signals (164,165). Peripheral nociceptive inputs inhibit the GRP-GRPR pathway by activating basic helix-loop-helix family member E22 interneurons, which reduces chemical itch. Somatostatin increases pruritus through binding to somatostatin 2 receptors, inhibiting dynorphinergic neurons and disinhibiting GRPR⁺ neurons (166,167).

Mechanical itch occurs when LTMRs in the skin activate excitatory urocortin 3⁺ or neuropeptide Y (NPY) receptor Y1⁺ interneurons, which can be inhibited by NPY⁺ inhibitory interneurons (75,168). Mechanical itch is transmitted by spinal-parabrachial calcitonin receptor-like receptor/homeobox gene LBX1 (LBX1)-positive projection neurons, while chemical itch is partially mediated by tachykinin

Table IV. Functional mechanisms of perioestin and neurotrophic factors in pruritus.

Designation	Pathological expression	Disease association	Mechanism of action	Pruritus regulation features	Therapeutic potential	(Refs.)
Perioestin	Expressing cells: Keratinocytes and fibroblasts	Prurigo nodularis: Dermal staining intensity exhibits a positive association with pruritus severity; Bullous pemphigoid: Associated with pruritic intensity, eosinophil infiltration and IL-13 ⁺ cell presence; AD: Lesional skin and serum levels are positively associated with disease severity	i) Direct pathway: Stimulates sensory nerve fibers; and ii) indirect pathway: Activates immune/non-immune cells (such as mast cells and eosinophils) through integrin receptors (such as $\alpha\beta3/\beta5$), leading to the release of pruritogenic mediators	Drives persistent pruritus in chronic inflammatory skin diseases (AD, PN and Bullous Pemphigoid (BP))	Potential therapeutic target: Inhibition of perioestin or its integrin receptors may suppress neural activation and immune amplification	(146-148)
NGF	Elevated expression sites: Lesional epidermis and neurons (CTCL, Prurigo Nodularis (PN), psoriasis, AD and dermatomyositis); serum (in patients with pruritus without primary skin lesions)	Positively associated with pruritus severity in Sézary syndrome, AD and psoriasis	i) Activates the TRKA receptor on sensory neurons, potentiating neuronal excitability; and ii) increases cutaneous innervation density. Specificity: Selectively enhances itch evoked by cowhage spicules, with no effect on histamine-, BAM8-22-, β -ALA- or ET-1-induced pruritus	Synergistically promotes neural reorganization and neuronal sensitization, facilitating the progression of chronic pruritus	Interventional evidence: Anti-NGF (targeting TRKA) attenuates scratching behavior in AD models; therapeutic target: TRKA antagonists	(149-152)
BDNF	Elevated expression sites: Serum, plasma and eosinophils in patients with AD	Associated with the severity of childhood AD; however, exhibits no statistically significant association with pruritus intensity	Upregulates the expression levels of p75NTR/TRKA-C receptors on eosinophils, thereby enhancing their chemotactic activity; promotes the accumulation of BDNF ⁺ eosinophils in dermal regions with dense nerve fiber innervation, establishing a 'neuro-immune interactive' network	Participates indirectly in AD-associated pruritus through the chemotaxis and activation of immune cells (eosinophils), thereby synergizing with NGF to promote neurogenic inflammation	Potential therapeutic target: Disruption of the BDNF/p75NTR/TRK axis or inhibition of the neuronal chemotaxis of eosinophils may alleviate pruritus in AD	(153)

NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; AD, atopic dermatitis; TRK, neurotrophic receptor tyrosine kinase; p75NTR, p75 neurotrophin receptor; CTCL, cutaneous T cell lymphoma; BAM, bovine adrenal medulla; β -ALA, β -alanine; ET-1, endothelin 1.

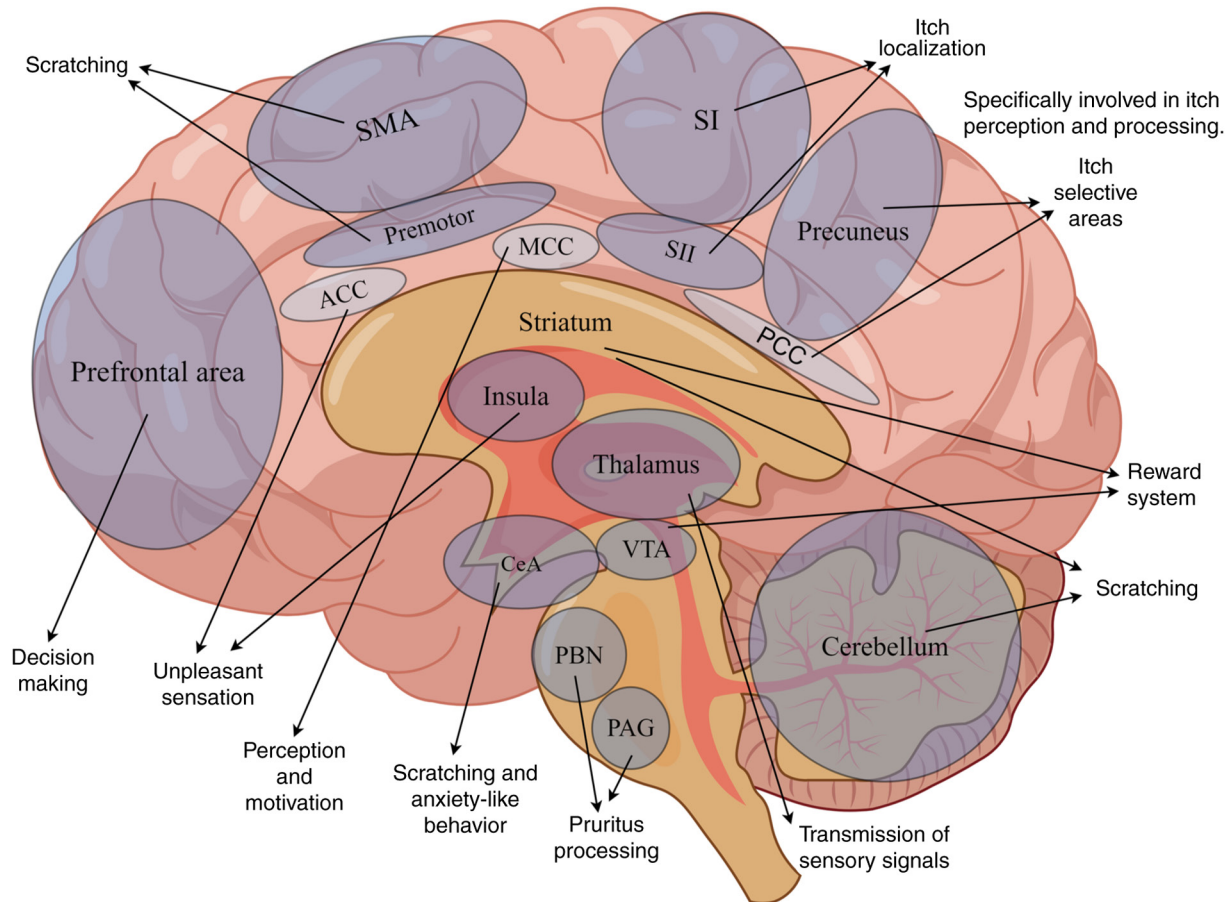


Figure 4. Brain regions associated with itch localization, perception and motivation. SI, primary somatosensory cortex; SII, secondary somatosensory cortex; CeA, central amygdala; VTA, ventral tegmental area; PAG, periaqueductal gray matter; PBN, parabrachial nucleus; PCC, posterior cingulate cortex; SMA, supplementary motor area; MCC, midcingulate cortex; ACC, anterior cingulate cortex.

precursor 1(TAC1)/LBX1-positive neurons (169,170). These findings support the ‘labeled line theory’ of modality-specific itch transmission.

In pruritus research, the labelled line theory posits that peripheral pruriceptors, specific receptors/ion channels, spinal interneurons, ascending projection pathways and cortical neurons form a dedicated ‘labelled’ pathway responsible for itch signal recognition, transmission and perception. This pathway diverges from other sensory modalities like pain at critical nodes, explaining phenomena such as scratching alleviating itch while exacerbating pain. For instance, itch and pain share certain mediators (e.g., IL-33, TRP channels) but exhibit modality-specific differences: IL-31/periostin predominantly drive pruritus, whereas CCL2/CXCL dominate pain; μ -opioid receptor activation alleviates pain but worsens itch. These observations support the concept of partially overlapping yet functionally segregated pathways (156). The theory also guides targeted therapies: Dupilumab targets Th2-associated pruritus (171), Nalfurafine acts on the GRPR pathway (157) and gabapentin addresses neuropathic itch (8), all reflecting the ‘pathway-specific treatment’ paradigm.

Brain networks and behavioral regulation. Perceptions of pruritus involve interactions among numerous neural circuits within the brain (172), including the primary somatosensory cortex, thalamus, PBN, central amygdala (CeA), periaqueductal gray and ventral tegmental area (VTA), among other

regions (Fig. 4). The PBN constitutes a core hub for itch processing (173), where neurons are activated under histamine and CQ stimulation. Deletion of the glutamate transporter in this region reduces itch-related behaviors (174). The CeA integrates inputs from numerous brain regions to modulate itch-associated affective states. For example, histamine enhances neuronal activity in its projection zones and optogenetic activation of CeA neurons evokes scratching and anxiety-like behaviors (175). The VTA mediates itch-related aversion through γ -aminobutyric acid-ergic neurons, while its dopaminergic neurons are implicated in the rewarding effects of scratching (176). Furthermore, TAC1⁺ neurons in the lateral and ventrolateral periaqueductal gray regulate spinal pruriceptive transmission through the rostral ventromedial medulla pathway (176). Itch perception arises from the coordinated activity of distributed brain networks processing sensory (177), emotional (178) and cognitive components (179); however, the specific neural circuitry mechanisms require further elucidation to guide targeted therapies.

3. TCM

TCM has evolved a complete pathological understanding of pruritus throughout millennia of clinical practice (180,181), establishing a systematic etiological and mechanistic framework that is consistent with modern medical perspectives.

In TCM theory, pruritus is classified into the syndromes of itch-wind (yang-feng) or wind-induced pruritus (180), with its core pathogenesis scientifically interpreted as follows: External factors such as allergen exposure, parasitic infections or humid-hot environments disrupt the skin barrier integrity (stratum corneum dysfunction) and trigger localized inflammation (local inflammatory response) (182,183), leading to microcirculatory dysregulation and heightened neuronal excitability (184). Alternatively, prolonged skin dryness (xerosis), nutritional inadequacies or reduced epidermal barrier function (epidermal barrier impairment) cause keratinocyte dehydration (185), immune cell infiltration and secondary neurogenic inflammation (186), which results in persistent pruritus. This theoretical approach emphasizes symptom-based phenotypic categorization for individualized diagnosis, creating the pathophysiological groundwork for precision medicine in contemporary dermatology. These ideas are associated with the etiology-driven classification systems provided by the International Forum for the Study of Itch (11,187-189), which merge classical conceptions with modern scientific paradigms.

Current status of clinical research on TCM therapies for pruritus. Clinical research on TCM for pruritic disorders (including psoriasis, eczema, urticaria and AD) has primarily focused on integrating disease-based diagnosis with TCM pattern differentiation (190-193). A combined approach of internal and external therapies has demonstrated enhanced efficacy, whereby topical herbal formulations for eczema can precisely modulate immune responses (190), acupuncture or multi-herb formulas for urticaria show high response rates (191), and integrative TCM-Western medicine strategies for psoriasis improve therapeutic outcomes and support early management of comorbidities (192). In the treatment of AD, TCM emphasizes the use of topical herbal washes or ointments (193). These formulations not only alleviate severe itching and skin dryness but also improve skin barrier function, thereby delaying disease recurrence and reducing dependence on corticosteroids (190-193). These interventions not only alleviate symptoms and reduce recurrence but also minimize adverse effects (such as skin atrophy, pigmentation, increased infection susceptibility and relapse after discontinuation, limiting long-term relief) associated with conventional pharmacotherapies (such as glucocorticoids, immunosuppressants and biological agents, among others), highlighting the holistic advantages of TCM.

Active pharmaceutical ingredients derived from TCM represent a key component of modern TCM research, serving not only as the pharmacodynamic material basis of compound formulations but also as candidates for drug development. According to data from China's National Medical Products Administration (194), a number of TCM formulations (such as Yinxieling granules, Xiaofeng Zhiyang granules and Fushu Zhiyang ointment), have entered the market, demonstrating efficacy in treating a number of pruritic disorders. Concurrently, the International Traditional Medicine Clinical Trial Registry (195), highlights three primary trends in TCM anti-pruritic clinical research: i) An increased proportion of mechanism verification studies; ii) accelerated development of novel TCM-based drugs; and iii) a marked rise in multicenter trials. Numerous clinical trials are currently being conducted, including a randomized,

open-label, dose-finding, positive drug-controlled clinical trial evaluating the efficacy and safety of Jingfang mixture (ITMCTR2025000520) for chronic urticaria, a randomized, double-blind, placebo-controlled trial assessing Hefu Zhiyang lotion (ITMCTR2024000637) for chronic eczema, and a study investigating the regulation of antimicrobial peptides and *Staphylococcus aureus* colonization in AD by Guben Huashi formula (ITMCTR2025001890). These efforts reflect the growing integration of TCM with evidence-based methodologies to advance pruritus management.

Research regarding the mechanisms of action of single Chinese herbal medicines and their active constituents in the treatment of cutaneous pruritus. TCM has been used to treat skin itching for a long time (180,181). Li *et al* (196) performed a systematic analysis of classical TCM prescriptions for itch management using association rule mining with the classical Apriori algorithm, as well as entropy clustering techniques to handle complex system features and unsupervised hierarchical clustering for autonomous stratification. The findings revealed that anti-inflammatory and immunomodulatory herbs dominate anti-pruritic TCM formulations, with the top five most frequently prescribed herbs being *Rehmannia glutinosa* (fresh *Rehmannia* root), *Paeonia lactiflora* (red peony root), *Glycyrrhiza glabra* (licorice root), *Lonicera japonica* (honeysuckle flower) and *Forsythia suspensa* (*Forsythia* fruit). Research has revealed that these herbs exert synergistic therapeutic effects through anti-inflammatory and immunomodulatory pathways (196). Core active substances, such as *Rehmannia* polysaccharides and catalpol from *Rehmannia glutinosa* (197-199), paeoniflorin from *Paeonia lactiflora* (200-203) and liquiritigenin A from *Glycyrrhiza glabra* (204-206), employ numerous regulatory mechanisms to target pruritus-related signaling pathways and inflammatory mediators. These findings not only support the scientific basis of ancient TCM prescription principles (207), but also provide a foundation for current pharmacological interpretation of their mechanisms (208,209). The present review aims to lay the groundwork for an improved understanding of the systemic regulatory networks of TCM compound formulations in pruritus treatment. Based on these findings, the present review continues to highlight current research regarding TCM treatments for cutaneous itch.

Rehmannia glutinosa (sheng dihuang). *Rehmannia glutinosa*, a perennial herbaceous plant from the *Scrophulariaceae* family. Its main bioactive components, *Rehmannia* polysaccharides and catalpol, exhibit specific molecular targeting of TLR4-mediated chronic pruritus mechanisms (197). Catalpol inhibits lipopolysaccharide (LPS)-induced production of TNF- α , IL-1 β , IL-6 and prostaglandin E2 in RAW264.7 macrophages through blocking of the NF- κ B and MAPK signaling pathways (198). *Rehmannia* polysaccharides reduce LPS-induced IL-6 and TGF- β production in macrophages by inhibiting the activation of the AKT/ERK/JNK pathway (199). These effects further block the TLR4-activated MyD88/IRAK/TRAF6-IKK-NF- κ B/MAPK signaling pathway, reducing pro-inflammatory cytokine production and inflammatory cascades (210). This mechanistic data may establish a molecular basis for the use of *Rehmannia glutinosa*

to treat pruritus caused by inflammatory skin diseases such as AD and psoriasis.

Paeonia lactiflora (*chishao*). *Paeonia lactiflora*, the dried root of *Paeonia lactiflora* of the Ranunculaceae family. Paeoniflorin, its main bioactive component, exhibits marked therapeutic effects in inflammatory skin conditions such as psoriasis and allergic dermatitis (200,201). Paeoniflorin specifically targets the TSLP-mediated pruritic pathway, suppressing abnormal upregulation of TSLP and reversing IL-10 down-regulation. By regulating the TSLP/IL-10 axis (202,203), paeoniflorin efficiently inhibits TSLP-activated JAK/STAT signaling-driven inflammatory cascades and itch signal transmission. These findings provide molecular evidence that *Paeonia lactiflora* may help alleviate pruritus caused by inflammatory skin diseases such as AD and psoriasis.

Glycyrrhiza uralensis (*licorice*). *Glycyrrhiza uralensis*, the dried roots and rhizomes of *Glycyrrhiza uralensis*, *Glycyrrhiza glabra* or *Glycyrrhiza inflata* from the Fabaceae family. Its main bioactive component, licochalcone A (LCA), exhibits therapeutic effects by precisely targeting TRPV1-mediated neurogenic pruritus processes. LCA inhibits TRPV1 channel activation and CGRP production, thus lowering neuronal hyperexcitability (204). LCA suppresses phosphorylation of the JAK1/STAT3 proteins (205), leading to decreased expression of pro-inflammatory cytokines such as IL-6, TNF- α and IL-1 β . These effects efficiently inhibit TRPV1-activated itch signal transduction and inflammatory cascades, establishing a potential molecular basis for *Glycyrrhiza uralensis* in the treatment of pruritus associated with inflammatory skin diseases such as AD and allergic dermatitis (206).

Lonicera japonica (*jinyinhua*). *Lonicera japonica*, the dried flower buds or newly opened blossoms of *Lonicera japonica* (Thunb.) from the Caprifoliaceae family. Its main bioactive component, *Lonicera japonica* polysaccharide-2 (LJP-2), exhibits therapeutic effects by precisely targeting TLR4-mediated chronic pruritus pathways. LJP-2 binds to the extracellular domain of TLR4 and inhibits MyD88 dimerization as well as NF- κ B nuclear translocation (211). This reduces the activity of the NF- κ B/MAPK signaling pathway, leading to decreased expression of pro-inflammatory cytokines such as TNF- α and IL-6. Concurrently, LJP-2 triggers the p62/nuclear factor erythroid 2-related factor 2 pathway (212), which promotes NLR family pyrin domain containing 3 inflammasome breakdown. These effects efficiently inhibit TLR4-activated inflammatory cascades and itch signal transduction, suggesting that *Lonicera japonica* may alleviate pruritus associated with inflammatory skin diseases, including AD (213).

Forsythia suspensa (*lianqiao*). *Forsythia suspensa*, a dried fruit from the Oleaceae family. Its main bioactive component, *Forsythia* ester glycoside B, exhibits therapeutic effects by precisely targeting TRPV3-mediated pruritic processes. This chemical particularly inhibits aberrant TRPV3 channel activity (214), which includes mutations and carvacrol activation. In a carvacrol-activated TRPV3 mutant (G573S) model, forsythia ester glycoside B increased 293 cell survival and lowered scratching behavior triggered by chemical stimuli in dry skin (214). These effects efficiently inhibited TRPV3 aberrant activation-induced itch signaling and inflammatory

cascades. This mechanistic evidence establishes a molecular basis for the potential efficacy of *Forsythia suspensa* in treating acute and chronic pruritus, skin allergies and inflammatory dermatological diseases.

Overall, the aforementioned five classical active components of TCM have similar modes of action in the treatment of pruritus. These drugs target specific molecular nodes in pruritus pathways, such as TLR4, TSLP, TRPV1 and TRPV3, reducing downstream inflammatory signaling cascades such as NF- κ B/MAPK, JAK/STAT and JAK1/STAT3 (215). This multi-target regulation decreases pro-inflammatory cytokines (including TNF- α , IL-6 and IL-1 β) and modulates anti-inflammatory mediators (including IL-10) (216), thereby inhibiting inflammatory amplification and pruritic signal transmission. These findings establish the molecular basis for TCM's synergistic multi-target regulation of pruritus in inflammatory skin disorders such as atopic dermatitis (AD) and psoriasis, demonstrating its therapeutic advantage through a multi-component, multi-target, and multi-pathway approach.

Studies have indicated that active constituents from additional medicinal herbs, including *Saposhnikovia Radix* (217-219), *Dictamnii Cortex* (28,220), *Moutan Cortex* (221-223), *Scutellariae Radix* (224-227), *Sophorae flavescens Radix* (228-230), *Cicadae Periostracum* (231), *Cnidii Fructus* (232-235), *Thymi Herba* (236,237), *Sophorae tonkinensis Radix* (238-240), *Kochiae Fructus* (241-243), *Gentianae Radix* (244-246), *Tripterygii Radix* (247,248), *Arnebiae Radix* (249,250), *Tetradium ruticarpum* (251,252) and *Artemisia annua* (253,254), also exhibit notable therapeutic value in ameliorating cutaneous pruritus (Table V).

Research regarding the mechanisms of action of Chinese herbal formulae in the treatment of cutaneous pruritus. Chinese herbal formulae, as the primary interventional technique within the diagnostic and therapeutic systems of TCM (255), achieve total organism management by combining the actions of diverse elements (256). Combinatorial approaches used in multi-herb formulations are key in the dynamic principles of pattern discrimination and treatment (257). Si and Zhao (258) used bibliometric methods to systematically analyze the composition principles of pruritus-related formulae, identify core compatibility frameworks using frequency statistics and herb cluster analysis, and conduct a focused quantitative investigation of the distribution patterns and cluster associations of high-frequency drugs. The findings showed that traditional formulae such as Longdan Xiegan Tang (gentian liver-draining decoction), Danggui Yinzi (angelica decoction), Xiaofeng San (wind-dispersing powder), Dihuang Yinzi (*Rehmannia* decoction) and Liuwei Dihuang Tang (six-ingredient *Rehmannia* decoction) exhibited marked therapeutic benefits in the treatment of cutaneous pruritus. Their mechanisms of action are based on a mix of holistic pattern discrimination and modern medical technology, as well as the multitarget regulatory qualities of chemical formulations (259). Furthermore, modern modified formulae and refined classical prescriptions have shown clear therapeutic value in both mechanistic research and clinical practice (260-262) by precisely optimizing herbal compatibility ratios, demonstrating the systemic benefits of compound formulations in regulating complex pathological networks.

Table V. Mechanisms of action of single Chinese herbal medicines and their active constituents in the treatment of cutaneous pruritus.

Chinese herbal medicine	Active constituents	Primary pruritus mechanisms	Mechanism of action	(Refs.)
<i>Rehmannia glutinosa</i>	<i>Rehmannia</i> polysaccharide and catalpol	TLR4	Inhibits AKT/ERK/JNK signaling pathways, reducing the release of inflammatory cytokines; blocks the NF- κ B and MAPK pathways, downregulating TNF- α , IL-1 β and related mediators	(197-199)
<i>Paeonia actiflora</i>	Paeoniflorin	TSLP	Inhibition of the JAK2/STAT3 signaling pathway downregulates TSLP expression and upregulates the anti-inflammatory cytokine IL-10.	(200-203)
<i>Glycyrrhiza uralensis</i>	Licochalcone A	TRPV1	Inhibits the JAK1/STAT3 pathway and PDE4, activates the PKA pathway; synergistically suppresses TRPV1 channel activation and CGRP release; promotes barrier repair	(204-206)
<i>Lonicera japonica</i>	LJP-2	TLR4	Activates the p62/Nrf2 pathway to degrade the NLRP3 inflammasome; inhibits the TLR4/NF- κ B pathway, reducing TNF- α and IL-6 secretion	(211-213)
<i>Forsythia suspensa</i>	<i>Forsythia</i> ester glycoside B	TRPV3	Selectively inhibits TRPV3 channel activity to block pruritic signaling; restores skin barrier function	(214)
Saposhnikoviae Radix	Cimifugin	TRPV4, IL-13 and IL-33	Inhibits TRPV4 channel expression and reduces Th2 cytokine levels (IL-33 and IL-13); restores barrier proteins such as filaggrin	(217-219)
Dictamni Cortex	Dictamnine and fraxinellone	IL-4 and IL-31	Inhibits IL-4 and IL-31 expression; blocks the JAK1/STAT3/STAT6 pathway; modulates MRGPRA3/TRPA1/P2X3 receptor signaling	(28,220)
Moutan Cortex	Paeonol	TLR4 and IL-23/IL-17	Inhibits the IL-23/Th17 axis and JAK2/STAT3 phosphorylation; reduces pruritic mediators (β -endorphin and IL-4); antagonizes TLR4	(221-223)
Scutellariae Radix	Baicalein	TRPV3 and TSLP	Inhibits NF- κ B p65 phosphorylation to downregulate TSLP; blocks the STAT3/LCN2 cascade; selectively inhibits TRPV3 channel activity	(224-227)
<i>Sophorae flavescens</i> Radix	Matrine	TLR4 and TSLP	Inhibits inflammatory signaling pathways (such as the MAPK and STAT3 signaling pathways) and the expression of inflammatory cytokines (such as TNF- α and IL-6); downregulates TLR4 receptor activity; modulates Th1/Th2 immune balance; reduces serum total IgE and TSLP levels; suppresses immune cell infiltration (decreasing mast cell and eosinophil counts)	(228-230)

Table V. Continued.

Chinese herbal medicine	Active constituents	Primary pruritus mechanisms	Mechanism of action	(Refs.)
Cicadae Periostracum	Cicadae Periostracum extract	IL-4/IL-13	Blocks downstream inflammatory signaling, reduces production of IL-4, IL-13 and chemokines (TARC, MDC and RANTES); restores skin barrier function; decreases mast cell infiltration and serum IgE levels; downregulates NGF	(231)
Cnidii Fructus	Osthole	TRPV3, NG, SP, MRGPRX2, IL-4/13 and IL-33	Selectively blocks TRPV3 channels, inhibiting calcium influx and the release of inflammatory cytokines (such as TNF- α , IL-6 and IL-1 β) and neuropeptides (such as NGF and SP); targets MRGPRX2 receptors to suppress MAPK/ERK phosphorylation pathways, reducing mast cell degranulation, histamine release and Th2 cytokine production (IL-4/IL-5/IL-13); modulates the IL-33/ST2 signaling axis, inhibiting ILC2 activation and eosinophil chemotaxis	(232-235)
Thymi Herba	Thymol	TRPM8	Specifically activates the TRPM8 ion channel, inducing Ca ²⁺ influx to directly inhibit pruritic signaling; suppresses MAPK pathways (such as P38 and ERK phosphorylation) to reduce pro-inflammatory cytokine release (such as TNF- α and IL-1 β); modulates Th1/Th2 cytokine balance; inhibits mast cell infiltration and mitigates skin barrier damage	(236,237)
<i>Sophorae tonkinensis</i> Radix	Sophocarpine	TRPA1, TRPV1 and TLR4	Inhibits TRPA1 and TRPV1 channel activity; modulates the TLR4/NF- κ B/MAPK inflammatory signaling pathway to reduce pro-inflammatory cytokine release (TNF- α , IL-1 β and IL-6); regulates neural signaling and immune responses	(238-240)
Kochiae Fructus	Kochia saponin Ic and oleanolic acid glycoside	IL-23/IL-17	Inhibits the IL-23/IL-17 inflammatory axis and the Wnt/ β -catenin signaling pathway; downregulates the release of histamine, 5-HT and inflammatory cytokines (TNF- α , IL-1 β and IL-6); suppresses abnormal proliferation of HaCaT keratinocytes and induces their apoptosis	(241-243)
Gentianae Radix	Gentiopicroside	IL-17	Inhibits TNF- α -induced expression of pro-inflammatory cytokines (such as IL-6, IL-23A and IL-17A); modulates the NF- κ B/NLRP3/caspase-1 inflammatory signaling pathway; downregulates keratinocyte proliferation-associated protein K17 and angiogenesis factor VEGFA	(244-246)

Table V. Continued.

Chinese herbal medicine	Active constituents	Primary pruritus mechanisms	Mechanism of action	(Refs.)
Tripterygii Radix	Triptolide	TRPV1 and TLR4	Promotes SUMOylation of TRPV1, inhibits the physical interaction between histamine receptor H1R and TRPV1, and accelerates ubiquitin-mediated degradation of H1R; suppresses inflammation-related signaling pathways (for example, TLR, NF-κB, MAPK, JAK/STAT and PI3K/AKT/mTOR signaling pathways), reduces expression of pro-inflammatory cytokines (IL-12, IL-23 and TNF-α) and targets PTGS2 to regulate prostaglandin metabolism	(247,248)
Arnebiae Radix	Shikonin	IL-17	Inhibits mast cell activation and reduces expression of inflammatory cytokines (such as IL-4/13, IL-17A and TNF-α); blocks signaling pathways such as the TLR4/NF-κB and JAK/STAT3 signaling pathways; decreases histamine release and pruritus-associated neurotransmitter transmission	(249,250)
<i>Tetradium ruticarpum</i>	Evodiamine/rutaecarpine	IL-17, TRPV1, TRPV3 and TRPV4	Inhibits TNF-α, IL-23 and IL-17A expression and reduces the levels of TRPV1/TRPV3/TRPV4 channels and pruritic mediators (SP, NGF and CGRP)	(251,252)
<i>Artemisia annua</i>	Dihydroartemisinin	IL-17	Inhibits NF-κB/MAPK activation, decreases pro-inflammatory cytokines (IL-17, IL-23, TNF-α and IL-6) and enhances TGF-β expression	(253,254)

TRPV, transient receptor potential vanilloid; TLR, toll-like receptor; TRPA, transient receptor potential ankyrin; TRPM, transient receptor potential melastatin; SP, substance P; MRGPR, Mas-related G protein-coupled receptor; TSLP, thymic stromal lymphopoietin; MyD88, myeloid differentiation primary response 88; PDE4, phosphodiesterase 4; NGF, nerve growth factor; PKA, protein kinase A; CGRP, calcitonin gene-related peptide; Nrf2, nuclear factor erythroid 2-related factor 2; NLRP3, NLR family pyrin domain containing 3; Th, T helper; P2X3, P2X purinoceptor 3; LCN2, lipocalin 2; 5-HT, 5-hydroxytryptamine; SUMO, small ubiquitin-like modifier; PTGS2, prostaglandin-endoperoxide synthase 2; LJP-2, *Lonicera japonica* polysaccharide-2; TARC, thymus and activation-regulated chemokine; ST2, IL-1 receptor-like 1; RANTES, regulated upon activation, normal T cell expressed and secreted; MDC, macrophage-derived chemokine; H1R, histamine H1 receptor; ILC2, type 2 Innate lymphoid cells; JAK, Janus kinase; NGF, nerve growth factor.

Longdan Xiegan decoction. Longdan Xiegan decoction, derived from the classical medical compendium *Yi Fang Ji Jie* (263), comprises 10 herbal components: *Gentiana scabra* (Longdancao), *Scutellaria baicalensis* (Huangqin), *Gardenia jasminoides* (Zhizi), *Alisma plantago-aquatica* (Zexie), *Plantago asiatica* (Cheqianzi), *Angelica sinensis* (Danggui), *Rehmannia glutinosa* (Dihuang), *Bupleurum chinense* (Chaihu), *Paeonia suffruticosa* (Mudanpi) and *Prunella vulgaris* (Xiakucao). The decoction significantly reduces ear swelling and skin pathology scores in eczematous rats while improving eczematological symptoms

such as erythema, papules, and vesicles. These effects suggest its capacity to inhibit H1R/TRPV1 and PAR-2/TRPV1 pathways, downregulate pruritic-related proteins (e.g., IL-31, TSLP), suppress p38MAPK phosphorylation, and reduce the activity of inflammatory signaling pathways such as NF-κB, thereby attenuating epidermal thickening, hyperkeratosis, and dermal edema (264).

Danggui Yinzi. Danggui Yinzi, originating from the Song dynasty medical text *Chong Ding Yan Shi Ji Sheng Fang* (265), consists of 10 herbal ingredients: *Angelica sinensis* (Danggui),

Paeonia lactiflora (Bai Shao), *Ligusticum chuanxiong* (Chuan Xiong), *Rehmannia glutinosa* (Sheng Di Huang), *Schizonepeta tenuifolia* (Jing Jie Sui), *Saposhnikovia divaricata* (Fang Feng), *Tribulus terrestris* (Bai Ji Li), *Polygonum multiflorum* (He Shou Wu), *Astragalus membranaceus* (Huang Qi) and *Glycyrrhiza uralensis* (Gan Cao). This formulation effectively targets the IL-33/ST2-mediated pruritic signaling pathway (266,267), inhibiting mast cell activation and degranulation. It also reduces the expression of mast cell tryptase and the release of pro-inflammatory cytokines such as TNF- α and IL-1 β (266). Furthermore, it corrects the Th1/Th2 immunological imbalance by upregulating IFN- γ , downregulating IL-4 and IgE, as well as decreasing the production of leukotrienes (LTs; including LTB4 and LTC4) and their receptors [cysteinyl (Cys)-leukotriene receptor 1 (LTR1) and CysLTR2] (267). These effects notably disrupt the IL-33-induced neuroimmune-epidermal crosstalk network, reducing inflammatory amplification loops and easing pathological alterations such as dermal edema, capillary dilatation and epidermal barrier failure. The molecular pharmacological profile of Danggui Yinzi provides a mechanistic basis for its therapeutic efficacy in chronic pruritic skin diseases such as urticaria, which is associated with the IL-33-driven Th2-type pruritic pathway.

Xiaofeng San. Xiao Feng San, derived from the Ming Dynasty medical text *Wai Ke Zheng Zong* authored by Chen Shigong, is among the most widely applied traditional Chinese medicine formulas in dermatological clinical practice. It comprises 13 herbal ingredients: *Angelica sinensis* (Danggui), *Rehmannia glutinosa* (Sheng Di Huang), *Saposhnikovia divaricata* (Fang Feng), Cicadae periostracum (Chan Tui), Anemarrhena asphodeloides (Zhi Mu), Gypsum fibrosum (Shi Gao), *Sophora flavescens* (Ku Shen), *Akebia quinata* (Mu Tong), *Schizonepeta tenuifolia* (Jing Jie), *Arctium lappa* (Niu Bang Zi), *Atractylodes lancea* (Cang Zhu), *Sesamum indicum* (Hu Ma), and *Glycyrrhiza uralensis* (Gan Cao). This formulation exerts anti-pruritic effects by precisely targeting IL-31/oncostatin-M receptor- β (OSMR β)- and IL-33/ST2-mediated Th2-type chronic pruritus mechanisms (268). It markedly reduces serum levels of IL-31, IL-33 and IgE, and suppresses IL-17 release (269). Furthermore, it upregulates aquaporin-3 expression to restore epidermal barrier integrity (270). These actions effectively block the activation of the JAK/STAT, MAPK and NF- κ B signaling pathways triggered by IL-31 and IL-33 (133,271-273), thereby inhibiting keratinocyte inflammation, mast cell degranulation and the neuroimmune-epidermal crosstalk-driven pruritic amplification cycle (16). This mechanistic framework provides a molecular basis for Xiaofeng San's therapeutic efficacy in treating Th2-dominated chronic pruritic disorders such as AD, directly aligning with the pathogenic role of IL-31/IL-33-activated neuroimmune-inflammatory networks.

These three TCM formulations contribute to curing Th2-type pruritus by targeting key cytokine pathways, including the TSLP/TSLPR/IL-7R α , IL-31/OSMR β and IL-33/ST2 signaling axes (133,271). This multi-target approach disrupts the inflammatory amplification cycle in the 'neuro-immuno-epidermal' crosstalk network and inhibits key signaling pathways, including the JAK/STAT, MAPK and NF- κ B signaling pathways (272,273). As a result, these

formulations demonstrate a coordinated reduction in mast cell activation, keratinocyte dysfunction and skin barrier deterioration (16). These findings provide the groundwork for multi-target synergistic intervention in Th2-driven chronic pruritic dermatoses such as AD and urticaria, determining the TCM therapeutic premise of systemic control through multi-pathway synergy.

In addition to the aforementioned Chinese herbal formulae, other compound prescriptions such as Guizhi Mahuang Ge Ban Tang (274) (cinnamon and *Ephedra* half-and-half decoction), Taohong Siwu Tang (275) (peach kernel and *Carthamus* four-substance decoction), Huanglian Jiedu Tang (276,277) (*Coptis* toxin-resolving decoction), Jiawei Guomin Jian (278-281) (modified allergy-relieving decoction), Danggui Kushen Wan (282,283) (*Angelica* and *Sophora* pill), Jiuwei Yong'an Granule (284) (nine-ingredient Yong'an granule) and Yupingfeng San (285,286) (jade wind-barrier powder) have also been demonstrated to alleviate cutaneous pruritus (Table VI).

4. Conclusion

The present review provides a systematic review of the diversity and complexity of pruritus mechanisms, with a focus on the multi-pathway inhibition of pruritic signaling by active components of single Chinese herbs and compound formulations through synergistic modulation of the 'neuro-immune-cutaneous' interaction network, specifically the following interventions: i) Suppression of receptor activation (including PARs and MRGPRs) and subsequent sensitization of downstream TRP channels; ii) inhibition of cytokine-mediated Th2 immune bias (for example, IL-4, IL-13 and IL-31) and mast cell degranulation; and iii) promotion of epidermal barrier repair (particularly in compound formulations). These findings provide notable mechanistic evidence to support TCM multi-target and holistic therapeutic strategies for pruritus. Herbal components work synergistically to regulate peripheral signaling and central integration, making them safer compared with single-target therapy for interrupting the 'itch-scratch-inflammation' cycle (287).

However, certain limitations remain. Firstly, interactions between components within compound formulations are not fully understood and the clinical applicability of existing experimental models needs to be validated by larger-sample clinical trials. Future studies should aim to explore novel pruritus-associated signaling pathways, multi-target synergistic therapies and combined Chinese-Western therapeutic techniques to improve overall efficacy.

The following suggestions represent treatment approaches combining TCM and Western medicine: Firstly, following the TCM principles of therapeutic customization and symptom distinction may improve clinical outcomes. Future research should aim to build upon conventional approaches while actively investigating novel interventions and technologies. For example, modern biotechnology could be utilized to enhance herbal extraction and formulation techniques, thereby creating next-generation herbal preparations. Similarly, the integration of external TCM therapies such as acupuncture, cupping and herbal bathing with contemporary physical therapies should be considered. Secondly, further collaboration between TCM

Table VI. Mechanisms of action of Chinese herbal formulae in the treatment of cutaneous pruritus.

Compound formula	Composition	Primary pruritus mechanisms	Mechanism of action	(Refs.)
Longdan Xiegan decoction	<i>Gentiana scabra</i> , <i>Scutellaria baicalensis</i> , <i>Gardenia jasminoides</i> , <i>Alisma plantago-aquatica</i> , <i>Plantago asiatica</i> , <i>Angelica sinensis</i> , <i>Rehmannia glutinosa</i> , <i>Bupleurum chinense</i> , <i>Paeonia suffruticosa</i> and <i>Prunella vulgaris</i>	TSLP/TSLPR/IL-7R α	Inhibits H1R/TRPV1 and PAR-2/TRPV1 pathways; reduces expression of pruritus-associated proteins; suppresses p38 MAPK phosphorylation; attenuates inflammatory signaling pathway activity	(263,264)
Danggui Yinzi	<i>Angelica sinensis</i> , <i>Paeonia lactiflora</i> , <i>Ligusticum chuanxiong</i> , <i>Rehmannia glutinosa</i> , <i>Schizonepeta tenuifolia</i> , <i>Saposhnikovia divaricata</i> , <i>Tribulus terrestris</i> , <i>Polygonum multiflorum</i> , <i>Astragalus membranaceus</i> , and <i>Glycyrrhiza uralensis</i>	IL-33	Inhibits mast cell activation and degranulation; reduces expression of degranulation marker MCT protein; likely mediated through suppression of IL-33 signaling and downstream cytokine secretion (TNF- α and IL-1 β)	(265-267)
Xiaofeng San	<i>Angelica sinensis</i> , <i>Rehmannia glutinosa</i> , <i>Saposhnikovia divaricata</i> , <i>Cicadae periostracum</i> , <i>Anemarrhena asphodeloides</i> , <i>Gypsum fibrosum</i> , <i>Sophora flavescens</i> , <i>Akebia quinata</i> , <i>Schizonepeta tenuifolia</i> , <i>Arctium lappa</i> , <i>Atractylodes lancea</i> and <i>Sesamum indicum</i>	IL-31 and IL-33	Reduces serum levels of IL-31, IL-33 and IgE; improves clinical efficacy, potentially through immunomodulatory and anti-inflammatory mechanisms	(269,270)
Guizhi Mahuang Ge Ban Tang	<i>Cinnamomum cassia</i> , <i>Paeonia lactiflora</i> , <i>Zingiber officinale</i> , <i>Glycyrrhiza uralensis</i> , <i>Ephedra sinica</i> , <i>Ziziphus jujuba</i> and <i>Prunus armeniaca</i>	IL-17	Core targets include IL-6, TNF, JUN, VEGFA and MAPK8; exerts antibacterial, anti-inflammatory, immunosuppressive and antioxidant effects by modulating AGE-RAGE, fluid shear stress, TNF and IL-17 signaling pathways	(274)
Taohong Siwu Tang	<i>Prunus persica</i> , <i>Carthamus tinctorius</i> , <i>Ligusticum chuanxiong</i> , <i>Angelica sinensis</i> , <i>Paeonia veitchii</i> and <i>Rehmannia glutinosa</i>	IL-17	Modulates targets including caspase-3, IL-6, VEGFA, ESR1 and EGFR; regulates IL-17, TNF, MAPK, PI3K/AKT and JAK/STAT signaling pathways and modulates Th17 cell differentiation	(275)
Huanglian Jiedu Tang	<i>Coptis chinensis</i> , <i>Scutellaria baicalensis</i> , <i>Phellodendron chinense</i> and <i>Gardenia jasminoides</i>	TSLP	Downregulates mRNA expression of IL-13, IL-31, HRH4 and TSLP; inhibits the release of pro-inflammatory cytokines (IL-6, IL-1 β and TNF- α); blocks the TLR4/NF- κ B inflammatory signaling pathway and NLRP3 inflammasome activation, thereby suppressing inflammatory responses	(276,277)
Jiawei Guomin Jian	<i>Tellaria dichotoma</i> , <i>Prunus mume</i> , <i>Saposhnikovia divaricata</i> , <i>Schisandra chinensis</i> , <i>Glycyrrhiza uralensis</i> (with	IL-4/IL-13/IL-33	Inhibits mast cell degranulation and its autoamplification effects; modulates the IgE/Fc ϵ RI/MAPK	(278-281)

Table VI. Continued.

Compound formula	Composition	Primary pruritus mechanisms	Mechanism of action	(Refs.)
	additions: <i>Dictamnus dasycarpus</i> and <i>Cryptotympana pustulata</i>)		signaling pathway; reduces the release of pruritogenic factors (such as histamine, MCT, IL-4, IL-13 and IL-33); downregulates the expression of pruritus-promoting receptors (H1R, H4R and PAR-2) while upregulating the activity of the anti-inflammatory receptor H2R	
Danggui Kushen Wan	<i>Sophora flavescens</i> and <i>Angelica sinensis</i>	IL-4, IL-13 and TSLP	Inhibits mast cell degranulation and the release of histamine/tryptase; modulates JAK/STAT and IL-17 signaling pathways; reduces the expression of Th2 cytokines (IL-4, IL-13 and TSLP); exerts anti-inflammatory and immunomodulatory effects	(282,283)
Jiuwei Yong'an granule	<i>Smilax glabra</i> , <i>Rehmannia glutinosa</i> , <i>Plantago asiatica</i> , <i>Isatis indigotica</i> , <i>Forsythia suspensa</i> , <i>Alisma orientale</i> , <i>Angelica sinensis</i> , <i>Dioscorea opposita</i> and <i>Dioscorea hypoglauca</i>	IL-4, IL-13, IL-31 and IL-33	Reduces serum levels of IgE, TNF- α , IL-1 β , IL-4, IL-13, IL-31, IL-33 and IFN- γ ; ameliorates skin lesion pathology	(284)
Yuping-feng San	<i>Astragalus membranaceus</i> , <i>Atractylodes macrocephala</i> and <i>Saposhnikovia divaricata</i>	Th2 inflammatory axis	Ameliorates cutaneous barrier integrity; reduces infiltration of inflammatory cells and mast cells; inhibits Langerhans cell activation and downregulates CD1a and IL-31 expression; decreases levels of inflammatory mediators (CRP, IL-17 and TNF- α); modulates Th2 immune responses	(285,286)

TSLP, thymic stromal lymphopoietin; R α , receptor α , TRPV, transient receptor potential vanilloid; Th, T helper; AGE, advanced glycation end-products; RAGE, receptor of AGE; HR, histamine receptor; NLRP3, NLR family pyrin domain containing 3; PAR, protease-activated receptor; Fc ϵ RI, Fc ϵ receptor I; MCT, mast cell tryptase; JAK, Janus kinase; TSLPR, TSLP receptor; HRH4, histamine H4 receptor; CRP, C-reactive protein; ESR1, estrogen receptor 1.

and Western medical professionals is necessary to capitalize on the advantages of the other. To maximize holistic regulation, lower recurrence rates, increase treatment efficacy and improve the quality of life of patients with chronic diseases, standardized, evidence-based diagnostic and therapeutic protocols must be established. These integrated methods seek to ensure clinical rigor and translational relevance in current healthcare systems by bridging the gap between established clinical practices and evidence-based standards.

To ensure scientific rigor and the preservation of TCM characteristics, randomized controlled trials (RCTs) combining TCM and Western medicine should strictly

adhere to randomization, control and blinding principles (288,289) while fully integrating TCM's syndrome differentiation framework into treatment protocols. Specific strategies include core grouping criteria based on TCM syndrome differentiation and using clear (290), standardized syndrome diagnostic criteria as the primary stratification component, rather than relying primarily on Western disease categories. Blinding implementation requires developing placebos that are comparable in appearance, flavor and taste to active herbal medicines, as well as keeping outcome assessors blind to group allocation to increase objectivity (291). To guarantee acceptable statistical power, the sample size

should be determined using mixed-effects models for continuous variables (for example, pruritus ratings) and χ^2 tests for categorical outcomes (292). Multicenter coordination requires unifying inclusion/exclusion criteria, diagnostic methodologies and treatment processes across centers, as well as centralizing training and developing a robust quality control system to improve sample representativeness and result dependability (293). Outcome metrics include clinical indicators, quality-of-life assessments and TCM-specific syndrome scores, which may help capture treatment outcomes properly (294). To address common issues, standardized syndrome differentiation training must be implemented to ensure diagnostic consistency (295), thereby establishing clear protocols for treatment frequency, procedural standardization and adherence optimization (for example, rationalizing treatment schedules and improving follow-up). These efforts seek to standardize and modernize TCM RCTs, increasing their scientific validity and reputation.

Emerging technologies present promising prospects for mechanistic study and medication development. Structural biology and multi-omics methods, such as cryo-electron microscopy and single-cell sequencing, can identify molecular connections between herbal components and pruritic targets. Artificial intelligence and metabolomics can clarify the holistic effects, compatibility principles and pharmacodynamic material basis of compound formulations. International multicenter RCTs will establish more evidence-based efficacy evaluation systems. Exploring developing domains (such as skin microbiota and epigenetics) may improve the understanding of TCM mechanisms in controlling 'neuro-immune-microecological' cross-system interactions.

These advancements present novel possibilities for combining Chinese and Western medicine in pruritus therapy, stressing the necessity of multi-target and systemic approaches. TCM is well-positioned to provide more systematic and accurate solutions for global pruritus regulation through interdisciplinary collaboration and technological integration, as well as strong scientific support for developing integrated diagnostic and treatment paradigms.

Acknowledgements

The figures were generated using FigDraw2.0 (www.figdraw.com).

Funding

The present study was supported by The Li Yongji National Master Traditional Pharmacist Legacy Studio Initiative (grant no. 14061240013) and The Open Project of the State Key Laboratory for Innovation and Integration of Classical Formulations and Modern Chinese Medicine (grant no. LSLSKL20240403).

Availability of data and materials

Not applicable.

Authors' contributions

HZ wrote, reviewed and edited the original draft. HZ was also responsible for conceptualization, conducting the investigation

and contributing towards the resources used. YoL conducted project administration, provided supervision and contributed towards the resources used, and writing, reviewing and editing of the manuscript. YuL conceptualized the present study, curated the data, conducted the investigation, and wrote, reviewed and edited the manuscript. DF, LZ and RC conceptualized the study, and contributed towards conducting the investigation, the resources used, and writing, reviewing and editing of the manuscript. XZ and JD acquired the funding and contributed towards conceptualizing the present study, conducting the investigation, the resources used, and writing, reviewing and editing of the manuscript. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools (Grammarly) were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Whang KA, Khanna R, Williams KA, Mahadevan V, Semenov Y and Kwatra SG: Health-related QOL and economic burden of chronic pruritus. *J Invest Dermatol* 141: 754-760.e1, 2021.
2. Feng J, Zhao Y, Xie Z, Zang K, Sviben S, Hu X, Fitzpatrick JAJ, Wen L, Liu Y, Wang T, *et al*: Miswiring of merkel cell and pruriceptive C fiber drives the itch-scratch cycle. *Sci Transl Med* 14: eabn4819, 2022.
3. Wimalasena NK, Milner G, Silva R, Vuong C, Zhang Z, Bautista DM and Woolf CJ: Dissecting the precise nature of itch-evoked scratching. *Neuron* 109: 3075-3087.e2, 2021.
4. Hu J, Zhao Q, Che D, Peng B, Wang X, Wang K, Li L and Geng S: Epidermal mechanical scratching-induced ROS exacerbates the itch-scratch cycle via TRPA1 activation on mast cells in atopic dermatitis. *J Invest Dermatol* 145: 2034-2048.e7, 2025.
5. Kahremany S, Hofmann L, Gruzman A and Cohen G: Advances in understanding the initial steps of pruritoceptive itch: How the itch hits the switch. *Int J Mol Sci* 21: 4883, 2020.
6. Huet F, Taieb C, Corgibet F, Brenaut E, Richard MA and Misery L: Pruritus, pain, and depression associated with the most common skin diseases: Data from the french study 'objectifs peau.' *Dermatol (Basel Switz)* 238: 448-453, 2022.
7. Kwatra SG, Kambala A and Dong X: Neuropathic pruritus. *J Allergy Clin Immunol* 152: 36-38, 2023.
8. Butler DC, Berger T, Elmariah S, Kim B, Chisolm S, Kwatra SG, Mollanazar N and Yosipovitch G: Chronic pruritus: A review. *JAMA* 331: 2114-2124, 2024.
9. Steinhoff M, Al-Khawaga S and Buddenkotte J: Itch in elderly patients: Origin, diagnostics, management. *J Allergy Clin Immunol* 152: 42-49, 2023.

10. Local Burden of Disease Household Air Pollution Collaborators: Mapping development and health effects of cooking with solid fuels in low-income and middle-income countries, 2000-18: A geospatial modelling study. *Lancet Glob Health* 10: e1395-e1411, 2022.
11. Misery L, Pierre O, Le Gall-Ianotto C, Lebonvallet N, Chernyshov PV, Le Garrec R and Talagas M: Basic mechanisms of itch. *J Allergy Clin Immunol* 152: 11-23, 2023.
12. Butala S and Paller AS: Optimizing topical management of atopic dermatitis. *Ann Allergy Asthma Immunol* 128: 488-504, 2022.
13. Lin J, Yu H, Huang Y, Yuan J, Wang C and Bai B: Bacterial cellulose membrane integrating phase-transited lysozyme nanofilm loaded with biguanides for dressing treatment of atopic dermatitis. *Int J Biol Macromol* 323: 147047, 2025.
14. Kim Y, Park K and Kim MS: Recent advances in polymer-based drug delivery systems for atopic dermatitis: Enhancing therapeutic efficacy and outcomes. *Mater Today Bio* 35: 102517, 2025.
15. Sum CH, Ching J, Zhang H, Loo S, Lo CW, Lai MK, Cheong PK, Yu CL and Lin ZX: Integrated Chinese and western medicine interventions for atopic dermatitis: A systematic review and meta-analysis. *Chin Med* 16: 101-116, 2021.
16. Li D, Han Y, Zhou J, Yang H, Chen J, Tey HL and Tan TTY: Mast cell-neuron axis as a core mechanism in chronic pruritus of atopic dermatitis: From mechanistic insights to therapeutic targets. *Front Immunol* 16: 1645095, 2025.
17. Song J, Xian D, Yang L, Xiong X, Lai R and Zhong J: Pruritus: Progress toward pathogenesis and treatment. *Biomed Res Int* 2018: 9625936, 2018.
18. Chinese guidelines for the management of chronic pruritus (2018). *Int J Dermatol Venereol* 3: 1-7, 2020.
19. Sutaria N, Adawi W, Goldberg R, Roh YS, Choi J and Kwatra SG: Itch: Pathogenesis and treatment. *J Am Acad Dermatol* 86: 17-34, 2022.
20. Agelopoulos K, Pereira MP, Wiegmann H and Ständer S: Cutaneous neuroimmune crosstalk in pruritus. *Trends Mol Med* 28: 452-462, 2022.
21. Shin J, Kim B and Jang S: *Diospyros lotus* leaf extract and its main component, myricitrin, inhibit both histamine-dependent and histamine-independent itching. *Exp Ther Med* 29: 121, 2025.
22. Guo L, Zhang Y, Fang G, Tie L, Zhuang Y, Xue C, Liu Q, Zhang M, Zhu K, You C, *et al*: Ligand recognition and G protein coupling of the human Itch receptor MRGPRX1. *Nat Commun* 14: 5004, 2023.
23. De Logu F, Maglie R, Titiz M, Poli G, Landini L, Marini M, Souza Monteiro de Araujo D, De Siena G, Montini M, Cabrini DA, *et al*: miRNA-203b-3p induces acute and chronic pruritus through 5-HTR2B and TRPV4. *J Invest Dermatol* 143: 142-153.e10, 2023.
24. Gan B, Yu L, Yang H, Jiao H, Pang B, Chen Y, Wang C, Lv R, Hu H, Cao Z and Ren R: Mechanism of agonist-induced activation of the human itch receptor MRGPRX1. *PLoS Biol* 21: e3001975, 2023.
25. Suzuki S, Iida M, Hiroaki Y, Tanaka K, Kawamoto A, Kato T and Oshima A: Structural insight into the activation mechanism of MrgD with heterotrimeric gi-protein revealed by cryo-EM. *Commun Biol* 5: 707, 2022.
26. Wolf K, Kühn H, Boehm F, Gebhardt L, Glaudo M, Agelopoulos K, Ständer S, Ectors P, Zahn D, Riedel YK, *et al*: A group of cationic amphiphilic drugs activates MRGPRX2 and induces scratching behavior in mice. *J Allergy Clin Immunol* 148: 506-522.e8, 2021.
27. In Kim H, Lee GB, Song DE, Sanjel B, Lee WJ and Shim WS: FSLRY-NH2, a protease-activated receptor 2 (PAR2) antagonist, activates mas-related G protein-coupled receptor C11 (MrgprC11) to induce scratching behaviors in mice. *Life Sci* 325: 121786, 2023.
28. Yang N, Shao H, Deng J, Yang Y, Tang Z, Wu G and Liu Y: Dictamnine ameliorates chronic itch in DNFB-induced atopic dermatitis mice via inhibiting MrgprA3. *Biochem Pharmacol* 208: 115368, 2023.
29. Al Hamwi G, Riedel YK, Clemens S, Namasivayam V, Thimm D and Müller CE: MAS-related G protein-coupled receptors X (MRGPRX): Orphan GPCRs with potential as targets for future drugs. *Pharmacol Ther* 238: 108259, 2022.
30. Fricke TC, Pantke S, Lüttmann B, Echtermeyer FG, Herzog C, Eberhardt MJ and Löffler A: Molecular mechanisms of MrgprA3-independent activation of the transient receptor potential ion channels TRPA1 and TRPV1 by chloroquine. *Br J Pharmacol* 180: 2214-2229, 2023.
31. Liu Q, Tang Z, Surdenikova L, Kim S, Patel KN, Kim A, Ru F, Guan Y, Weng HJ, Geng Y, *et al*: Sensory Neuron-Specific GPCR mrgprs are itch receptors mediating Chloroquine-induced pruritus. *Cell* 139: 1353-1365, 2009.
32. Lembo PMC, Grazzini E, Groblewski T, O'Donnell D, Roy MO, Zhang J, Hoffert C, Cao J, Schmidt R, Pelletier M, *et al*: Proenkephalin gene products activate a new family of sensory neuron-specific GPCRs. *Nat Neurosci* 5: 201-209, 2002.
33. Heller D, Doyle JR, Raman VS, Beinborn M, Kumar K and Kopin AS: Novel probes establish mas-related G protein-coupled receptor X1 variants as receptors with loss or gain of function. *J Pharmacol Exp Ther* 356: 276-283, 2016.
34. Guan Y, Liu Q, Tang Z, Raja SN, Anderson DJ and Dong X: Mas-related G-protein-coupled receptors inhibit pathological pain in mice. *Proc Natl Acad Sci* 107: 15933-15938, 2010.
35. Li Z, He SQ, Xu Q, Yang F, Tiwari V, Liu Q, Tang Z, Han L, Chu YX, Wang Y, *et al*: Activation of MrgC receptor inhibits N-type calcium channels in small-diameter primary sensory neurons in mice. *Pain* 155: 1613-1621, 2014.
36. Klein A, Solinski HJ, Malewicz NM, Jeong HF, Sypek EI, Shimada SG, Hartke TV, Wooten M, Wu G, Dong X, *et al*: Pruriception and neuronal coding in nociceptor subtypes in human and nonhuman primates. *Elife* 10: e64506, 2021.
37. Zhang S, Edwards TN, Chaudhri VK, Wu J, Cohen JA, Hirai T, Rittenhouse N, Schmitz EG, Zhou PY, McNeil BD, *et al*: Nonpeptidergic neurons suppress mast cells via glutamate to maintain skin homeostasis. *Cell* 184: 2151-2166.e16, 2021.
38. Wang C, Liu Y, Lanier M, Yeager A, Singh I, Gumpfer RH, Krumm BE, DeLeon C, Zhang S, Boehm M, *et al*: High-affinity agonists reveal recognition motifs for the MRGPRD GPCR. *Cell Rep* 43: 114942, 2024.
39. Liu Q, Sikand P, Ma C, Tang Z, Han L, Li Z, Sun S, LaMotte RH and Dong X: Mechanisms of itch evoked by β -alanine. *J Neurosci* 32: 14532-14537, 2012.
40. Christensen J, Vecchio S, Elberling J, Arendt-Nielsen L and Andersen H: Assessing punctate administration of beta-alanine as a potential human model of non-histaminergic itch. *Acta Derm Venereol* 99: 222-223, 2019.
41. Qu L, Fan N, Ma C, Wang T, Han L, Fu K, Wang Y, Shimada SG, Dong X and LaMotte RH: Enhanced excitability of MRGPRA3- and MRGPRD-positive nociceptors in a model of inflammatory itch and pain. *Brain* 137: 1039-1050, 2014.
42. Weisshaar E, Szepletowski JC, Dalgard FJ, Garcovich S, Gieler U, Giménez-Arnau AM, Lambert J, Leslie T, Mettang T, Misery L, *et al*: European S2k guideline on chronic pruritus. *Acta Derm Venereol* 99: 469-506, 2019.
43. Chompunud Na Ayudhya C, Roy S, Thapaliya M and Ali H: Roles of a mast Cell-specific receptor MRGPRX2 in host defense and inflammation. *J Dent Res* 99: 882-890, 2020.
44. Meixiong J, Anderson M, Limjunyawong N, Sabbagh MF, Hu E, Mack MR, Oetjen LK, Wang F, Kim BS and Dong X: Activation of mast-cell-expressed mas-related G-protein-coupled receptors drives non-histaminergic itch. *Immunity* 50: 1163-1171.e5, 2019.
45. Wang Z, Franke K, Bal G, Li Z, Zuberbier T and Babina M: MRGPRX2-Mediated degranulation of human skin mast cells requires the operation of *Gai*, *Gaq*, Ca^{++} Channels, ERK1/2 and PI3K-interconnection between early and late signaling. *Cells* 11: 953, 2022.
46. Treudler R and Simon J: Developments and perspectives in allergology. *J Dtsch Dermatol Ges* 21: 399-403, 2023.
47. Chaki S, Alkanfari I, Roy S, Amponnawarat A, Hui Y, Oskeritzian CA and Ali H: Inhibition of orai channel function regulates mas-related G protein-coupled receptor-mediated responses in mast cells. *Front Immunol* 12: 803335, 2022.
48. Thapaliya M, Chompunud Na Ayudhya C, Amponnawarat A, Roy S and Ali H: Mast cell-specific MRGPRX2: A key modulator of neuro-immune interaction in allergic diseases. *Curr Allergy Asthma Rep* 21: 3, 2021.
49. Jia T, Che D, Zheng Y, Zhang H, Li Y, Zhou T, Peng B, Du X, Zhu L, An J and Geng S: Mast cells initiate type 2 inflammation through tryptase released by MRGPRX2/MRGPRB2 activation in atopic dermatitis. *J Invest Dermatol* 144: 53-62.e2, 2024.
50. Kremer AE, Mayo MJ, Hirschfield GM, Levy C, Bowlus CL, Jones DE, Johnson JD, McWherter CA and Choi YJ: Seladelpar treatment reduces IL-31 and pruritus in patients with primary biliary cholangitis. *Hepatology* 80: 27-37, 2024.
51. Yu H, Zhao T, Liu S, Wu Q, Johnson O, Wu Z, Zhuang Z, Shi Y, Peng L, He R, *et al*: MRGPRX4 is a bile acid receptor for human cholestatic itch. *Elife* 8: e48431, 2019.

52. Meixiong J, Vasavda C, Green D, Zheng Q, Qi L, Kwatra SG, Hamilton JP, Snyder SH and Dong X: Identification of a bilirubin receptor that may mediate a component of cholestatic itch. *Elife* 8: e44116, 2019.
53. Meixiong J, Vasavda C, Snyder SH and Dong X: MRGPRX4 is a G protein-coupled receptor activated by bile acids that may contribute to cholestatic pruritus. *Proc Natl Acad Sci* 116: 10525-10530, 2019.
54. Meixiong J, Basso L, Dong X and Gaudenzio N: Nociceptor-mast cell sensory clusters as regulators of skin homeostasis. *Trends Neurosci* 43: 130-132, 2020.
55. Thibeault PE and Ramachandran R: Role of the helix-8 and C-terminal tail in regulating proteinase activated receptor 2 signaling. *ACS Pharmacol Transl Sci* 3: 868-882, 2020.
56. Fan M, Fan X, Lai Y, Chen J, Peng Y, Peng Y, Xiang L and Ma Y: Protease-activated receptor 2 in inflammatory skin disease: Current evidence and future perspectives. *Front Immunol* 15: 1448952, 2024.
57. Stefansson K, Brattsand M, Roosterman D, Kempkes C, Bocheva G, Steinhoff M and Egelrud T: Activation of proteinase-activated receptor-2 by human kallikrein-related peptidases. *J Invest Dermatol* 128: 18-25, 2008.
58. Deng L, Costa F, Blake KJ, Choi S, Chandrabalan A, Yousuf MS, Shiers S, Dubreuil D, Vega-Mendoza D, Rolland C, *et al*: S. aureus drives itch and scratch-induced skin damage through a V8 protease-PAR1 axis. *Cell* 186: 5375-5393.e25, 2023.
59. Chai Z, Zhou Y, Yang L, Zhang Y, Hossain S, Hajimirzaei S, Qi J, Zhang G, Wei Y and Li Z: MyD88 contributes to TLR3-mediated NF- κ B activation and cytokine production in macrophages. *Cells* 14: 1507, 2025.
60. Araldi D, Khomula EV, Bonet IJM, Bogen O, Green PG and Levine JD: Role of pattern recognition receptors in chemotherapy-induced neuropathic pain. *Brain* 147: 1025-1042, 2024.
61. Chen X, Zhang J, Wang Y, Hu Q, Zhao R, Zhong L, Zhan Q and Zhao L: Structure and immunostimulatory activity studies on two novel Flammulina velutipes polysaccharides: Revealing potential impacts of \rightarrow 6)- α -D-Glc p(1 \rightarrow) on the TLR-4/MyD88/NF- κ B pathway. *Food Funct* 15: 3507-3521, 2024.
62. Wei X, Sun W, Zhu P, Ou G, Zhang S, Li Y, Hu J, Qu X, Zhong Y, Yu W, *et al*: Refined polysaccharide from dendrobium devonianum resists H1N1 influenza viral infection in mice by activating immunity through the TLR4/MyD88/NF- κ B pathway. *Front Immunol* 13: 999945, 2022.
63. Feng Z, Meng R, Li Q, Li D and Xu Q: 5-aza-2'-deoxycytidine may regulate the inflammatory response of human odontoblast-like cells through the NF- κ B pathway. *Int Endod J* 54: 1105-1117, 2021.
64. Yang H, Wang YY, Chang W, Zhai M, Du WJ, Jiang W, Xiang YW, Qin G, Yu J, Gong Y and Han Q: Primary sensory neuron-derived miR-let-7b underlies stress-elicited psoriasis. *Brain Behav Immun* 123: 997-1010, 2025.
65. Liu X, Jiang J, Lin S, Ge W, Tao Q, Liu S, Zhanmu O, Yang Y, Chai B, Zhang J, *et al*: From skin to spinal cord: How IL-17a drives psoriatic chronic itch. *Brain Behav Immun* 132: 106218, 2026.
66. Liu T, Berta T, Xu ZZ, Park CK, Zhang L, Lü N, Liu Q, Liu Y, Gao YJ, Liu YC, *et al*: TLR3 deficiency impairs spinal cord synaptic transmission, central sensitization, and pruritus in mice. *J Clin Invest* 122: 2195-2207, 2012.
67. Moriyama M, Konno M, Serizawa K, Yuzawa N, Majima Y, Hayashi I, Suzuki T and Kainoh M: Anti-pruritic effect of isothiocyanates: Potential involvement of toll-like receptor 3 signaling. *Pharmacol Res Perspect* 10: e01038, 2022.
68. Min H, Lee H, Lim H, Jang YH, Chung SJ, Lee CJ and Lee SJ: TLR4 enhances histamine-mediated pruritus by potentiating TRPV1 activity. *Mol Brain* 7: 59, 2014.
69. Liu B, Escalera J, Balakrishna S, Fan L, Caceres AI, Robinson E, Sui A, McKay MC, McAlexander MA, Herrick CA and Jordt SE: TRPA1 controls inflammation and pruritogen responses in allergic contact dermatitis. *FASEB J* 27: 3549-3563, 2013.
70. Shiratori-Hayashi M, Koga K, Tozaki-Saitoh H, Kohro Y, Toyonaga H, Yamaguchi C, Hasegawa A, Nakahara T, Hachisuka J, Akira S, *et al*: STAT3-dependent reactive astrogliosis in the spinal dorsal horn underlies chronic itch. *Nat Med* 21: 927-931, 2015.
71. Koga K, Yamagata R, Kohno K, Yamane T, Shiratori-Hayashi M, Kohro Y, Tozaki-Saitoh H and Tsuda M: Sensitization of spinal itch transmission neurons in a mouse model of chronic itch requires an astrocytic factor. *J Allergy Clin Immunol* 145: 183-191.e10, 2020.
72. Feng J, Luo J, Mack MR, Yang P, Zhang F, Wang G, Gong X, Cai T, Mei Z, Kim BS, *et al*: The antimicrobial peptide human beta-defensin 2 promotes itch through toll-like receptor 4 signaling in mice. *J Allergy Clin Immunol* 140: 885-888.e6, 2017.
73. Kim HJ, Lee EH, Lim YH, Jeong D, Na HS and Jung Y: Pathophysiological role of TLR4 in chronic relapsing itch induced by subcutaneous capsaicin injection in neonatal rats. *Immune Netw* 22: e20, 2022.
74. Xu ZZ, Kim YH, Bang S, Zhang Y, Berta T, Wang F, Oh SB and Ji RR: Inhibition of mechanical allodynia in neuropathic pain by TLR5-mediated a-fiber blockade. *Nat Med* 21: 1326-1331, 2015.
75. Pan H, Fatima M, Li A, Lee H, Cai W, Horwitz L, Hor CC, Zaher N, Cin M, Slade H, *et al*: Identification of a spinal circuit for mechanical and persistent spontaneous itch. *Neuron* 103: 1135-1149.e6, 2019.
76. Chen O, Jiang C, Berta T, Powell Gray B, Furutani K, Sullenger BA and Ji RR: MicroRNA let-7b enhances spinal cord nociceptive synaptic transmission and induces acute and persistent pain through neuronal and microglial signaling. *Pain* 165: 1824-1839, 2024.
77. Proskocil BJ, Wai K, Lebold KM, Norgard MA, Michaelis KA, De La Torre U, Cook M, Marks DL, Fryer AD, Jacoby DB and Drake MG: TLR7 is expressed by support cells, but not sensory neurons, in ganglia. *J Neuroinflammation* 18: 209-222, 2021.
78. Liu X, Wang Y, Zeng Y, Wang D, Wen Y, Fan L, He Y, Zhang J, Sun W, Liu Y and Tao A: Microglia-neuron interactions promote chronic itch via the NLRP3-IL-1 β -GRPR axis. *Allergy* 78: 1570-1584, 2023.
79. Liu T, Xu ZZ, Park CK, Berta T and Ji RR: Toll-like receptor 7 mediates pruritus. *Nat Neurosci* 13: 1460-1462, 2010.
80. Park CK, Xu ZZ, Berta T, Han Q, Chen G, Liu XJ and Ji RR: Extracellular MicroRNAs activate nociceptor neurons to elicit pain via TLR7 and TRPA1. *Neuron* 82: 47-54, 2014.
81. Wang Z, Feng Y and Hu Q: Keratinocyte TLR2 and TLR7 contribute to chronic itch through pruritic cytokines and chemokines in mice. *J Cell Physiol* 238: 257-273, 2023.
82. Wu Y, Liu L, Bian C, Diao Q, Nisar MF, Jiang X, Bartsch JW, Zhong M, Hu X and Zhong JL: MicroRNA let-7b inhibits keratinocyte differentiation by targeting IL-6 mediated ERK signaling in psoriasis. *Cell Commun Signal* 16: 58, 2018.
83. Sanjel B, Kim BH, Song MH, Carstens E and Shim WS: Glucosylsphingosine evokes pruritus via activation of 5-HT2A receptor and TRPV4 in sensory neurons. *Br J Pharmacol* 179: 2193-2207, 2022.
84. Xie MX, Rao JH, Tian XY, Liu JK, Li X, Chen ZY, Cao Y, Chen AN, Shu HH and Zhang XL: ATF4 inhibits TRPV4 function and controls itch perception in rodents and nonhuman primates. *Pain* 165: 1840-1859, 2024.
85. Shirolkar P and Mishra SK: Role of TRP ion channels in pruritus. *Neurosci Lett* 768: 136379, 2022.
86. Hu Z, Zhang Y, Yu W, Li J, Yao J, Zhang J, Wang J and Wang C: Transient receptor potential ankyrin 1 (TRPA1) modulators: Recent update and future perspective. *Eur J Med Chem* 257: 115392, 2023.
87. Wilson SR, Gerhold KA, Bifolck-Fisher A, Liu Q, Patel KN, Dong X and Bautista DM: TRPA1 is required for histamine-independent, mas-related G protein-coupled receptor-mediated itch. *Nat Neurosci* 14: 595-602, 2011.
88. Hill XRZ, Morita XT, Brem XRB and Bautista XDM: S1PR3 mediates itch and pain via distinct TRP channel-dependent pathways. *J Neurosci* 38: 7833-7843, 2018.
89. Wilson SR, Nelson AM, Batia L, Morita T, Estandian D, Owens DM, Lumpkin EA and Bautista DM: The ion channel TRPA1 is required for chronic itch. *J Neurosci* 33: 9283-9294, 2013.
90. Mahmoud O, Soares GB and Yosipovitch G: Transient receptor potential channels and itch. *Int J Mol Sci* 24: 420, 2022.
91. Zhao J, Munanairi A, Liu XY, Zhang J, Hu L, Hu M, Bu D, Liu L, Xie Z, Kim BS, *et al*: PAR2 mediates itch via TRPV3 signaling in keratinocytes. *J Invest Dermatol* 140: 1524-1532, 2020.
92. Han Y, Luo A, Kamau PM, Takomthong P, Hu J, Boonyarat C, Luo L and Lai R: A plant-derived TRPV3 inhibitor suppresses pain and itch. *Br J Pharmacol* 178: 1669-1683, 2021.
93. Larkin C, Chen W, Szabó IL, Shan C, Dajnoki Z, Szegedi A, Buhl T, Fan Y, O'Neill S, Walls D, *et al*: Novel insights into the TRPV3-mediated itch in atopic dermatitis. *J Allergy Clin Immunol* 147: 1110-1114.e5, 2021.
94. Tsagareli MG, Follansbee T, Iodi Carstens M and Carstens E: Targeting transient receptor potential (TRP) channels, mas-related G-protein-coupled receptors (mrgprs), and protease-activated receptors (PARs) to relieve itch. *Pharmaceuticals (Basel)* 16: 1707, 2023.

95. Chen Y, Fang Q, Wang Z, Zhang JY, MacLeod AS, Hall RP and Liedtke WB: Transient receptor potential vanilloid 4 ion channel functions as a pruriceptor in epidermal keratinocytes to evoke histaminergic itch. *J Biol Chem* 291: 10252-10262, 2016.
96. Courtin AS and Mouraux A: Combining topical agonists with the recording of event-related brain potentials to probe the functional involvement of TRPM8, TRPA1 and TRPV1 in heat and cold transduction in the human skin. *J Pain* 23: 754-771, 2022.
97. Paricio-Montesinos R, Schwaller F, Udhayachandran A, Rau F, Walcher J, Evangelista R, Vriens J, Voets T, Poulet JFA and Lewin GR: The sensory coding of warm perception. *Neuron* 106: 830-841.e3, 2020.
98. Becker J, Ellerkmann CS, Schmelzer H, Hermann C, Lützel K, Gudermann T, Konrad DB, Trauner D, Storch U, Mederos Y and Schnitzler M: Optical control of TRPM8 channels with photo-switchable menthol. *Angew Chem Int Ed Engl* 64: e202416549, 2025.
99. Liu Y, Liu Y, Limjunyawong N, Narang C, Jamaldeen H, Yu S, Patiram S, Nie H, Caterina MJ, Dong X and Qu L: Sensory neuron-expressed TRPC3 mediates acute and chronic itch. *Pain* 164: 98-110, 2023.
100. Morita T, McClain SP, Batia LM, Pellegrino M, Wilson SR, Kienzler MA, Lyman K, Olsen AS, Wong JF, Stucky CL, *et al*: HTR7 mediates serotonergic acute and chronic itch. *Neuron* 87: 124-138, 2015.
101. Xie Z and Hu H: TRP channels as drug targets to relieve itch. *Pharmaceuticals (Basel)* 11: 1000, 2018.
102. Middleton SJ, Perini I, Themistocleous AC, Weir GA, McCann K, Barry AM, Marshall A, Lee M, Mayo LM, Bohic M, *et al*: Nav1.7 is required for normal C-low threshold mechanoreceptor function in humans and mice. *Brain* 145: 3637-3653, 2022.
103. Fauqueux J, Chaton L, Cleuziou P, Diependaële AS, Bach N, Gruchy N, Gerard M, Meneboob JP, Villenet C, Figeac M, *et al*: Long-read sequencing of recurrent *FGF12* duplications in epilepsy: Insights into structural mechanisms and aberrant isoforms. *Epilepsia* 66: 5014-5032, 2025.
104. Kühn H, Kappes L, Wolf K, Gebhardt L, Neurath MF, Reeh P, Fischer MJM and Kremer AE: Complementary roles of murine Nav1.7, Nav1.8 and Nav1.9 in acute itch signalling. *Sci Rep* 10: 2326, 2020.
105. Dong F, Shi H, Yang L, Xue H, Wei M, Zhong YQ, Bao L and Zhang X: FGF13 is required for Histamine-induced Itch sensation by interaction with Nav1.7. *J Neurosci* 40: 9589-9601, 2020.
106. Wiebe D, Limberg MM, Gray N and Raap U: Basophils in pruritic skin diseases. *Front Immunol* 14: 1213138, 2023.
107. Auyeung KL and Kim BS: Emerging concepts in neuropathic and neurogenic itch. *Ann Allergy Asthma Immunol* 131: 561-566, 2023.
108. Tang H, Hou T, Wang J and Zhou W: Research progress of histamine H₄ receptor and its antagonists. *Progress Pharmaceutical Sci* 48: 929-941, 2024 (In Chinese).
109. Nikolouli E, Mommert S, Dawodu DM, Schaper-Gerhardt K, Stark H, Dittrich-Breiholz O, Gutzmer R and Werfel T: The stimulation of TH2 cells results in increased IL-5 and IL-13 production via the H4 receptor. *Allergy* 79: 2186-2196, 2024.
110. Zhao ZQ, Liu XY, Jeffrey J, Karunarathne WK, Li JL, Munaniri A, Zhou XY, Li H, Sun YG, Wan L, *et al*: Descending control of itch transmission by the serotonergic system via 5-HT1A-facilitated GRP-GRPR signaling. *Neuron* 84: 821-834, 2014.
111. Stantcheva KK, Iovino L, Dhandapani R, Martinez C, Castaldi L, Nocchi L, Perlas E, Portulano C, Pesaresi M, Shirlekar KS, *et al*: A subpopulation of itch-sensing neurons marked by ret and somatostatin expression. *EMBO Rep* 17: 585-600, 2016.
112. Domocos D, Selescu T, Ceafalan LC, Iodi Carstens M, Carstens E and Babes A: Role of 5-HT1A and 5-HT3 receptors in serotonergic activation of sensory neurons in relation to itch and pain behavior in the rat. *J Neurosci Res* 98: 1999-2017, 2020.
113. Miyahara Y, Funahashi H, Haruta-Tsukamoto A, Kogoh Y, Kanemaru-Kawazoe A, Hirano Y, Nishimori T and Ishida Y: Differential contribution of 5-HT4, 5-HT5, and 5-HT6 receptors to acute pruriceptive processing induced by chloroquine and histamine in mice. *Biol Pharm Bull* 46: 1601-1608, 2023.
114. Liu BW, Li ZX, He ZG, Wang Q, Liu C, Zhang XW, Yang H and Xiang HB: Altered expression of itch-related mediators in the lower cervical spinal cord in mouse models of two types of chronic itch. *Int J Mol Med* 44: 835-846, 2019.
115. Bawazir M, Sutradhar S, Roy S and Ali H: MRGPRX2 facilitates IgE-mediated systemic anaphylaxis in a newly established knock-in mouse model. *J Allergy Clin Immunol* 155: 974-987.e1, 2025.
116. Bandyopadhyay M, Morelli AE, Balmert SC, Ward NL, Erdos G, Sumpter TL, Korkmaz E, Kaplan DH, Oberbarnscheidt MH, Tkacheva O, *et al*: Skin codelivery of contact sensitizers and neurokinin-1 receptor antagonists integrated in microneedle arrays suppresses allergic contact dermatitis. *J Allergy Clin Immunol* 150: 114-130, 2022.
117. Wang Z and Babina M: MRGPRX2 signals its importance in cutaneous mast cell biology: Does MRGPRX2 Connect mast cells and atopic dermatitis? *Exp Dermatol* 29: 1104-1111, 2020.
118. Liu AW, Zhang YR, Chen CS, Edwards TN, Ozyaman S, Ramcke T, McKendrick LM, Weiss ES, Gillis JE, Laughlin CR, *et al*: Scratching promotes allergic inflammation and host defense via neurogenic mast cell activation. *Science* 387: eadn9390, 2025.
119. Antúnez C, Torres MJ, López S, Rodríguez-Pena R, Blanca M, Mayorga C and Santamaría-Babi LF: Calcitonin gene-related peptide modulates interleukin-13 in circulating cutaneous lymphocyte-associated antigen-positive T cells in patients with atopic dermatitis. *Br J Dermatol* 161: 547-553, 2009.
120. Fassett MS, Braz JM, Castellanos CA, Salvatierra JJ, Sadeghi M, Yu X, Schroeder AW, Caston J, Munoz-Sandoval P, Roy S, *et al*: IL-31-dependent neurogenic inflammation restrains cutaneous type 2 immune response in allergic dermatitis. *Sci Immunol* 8: eabi6887, 2023.
121. Wheeler JJ, Williams N, Yu J and Mishra SK: Brain natriuretic peptide exerts inflammation and peripheral itch in a mouse model of atopic dermatitis. *J Invest Dermatol* 144: 705-707, 2024.
122. Wong LS, Yen YT, Lin SH and Lee CH: IL-17A induces endothelin-1 expression through p38 pathway in prurigo nodularis. *J Invest Dermatol* 140: 702-706.e2, 2020.
123. Ulzii D, Kido-Nakahara M, Nakahara T, Tsuji G, Furue K, Hashimoto-Hachiya A and Furue M: Scratching counteracts IL-13 signaling by upregulating the decoy receptor IL-13Rα2 in keratinocytes. *Int J Mol Sci* 20: 3324, 2019.
124. Wiegmann H, Renkhold L, Zeidler C, Agelopoulos K and Ständer S: Interleukin profiling in atopic dermatitis and chronic nodular prurigo. *Int J Mol Sci* 25: 8445, 2024.
125. Guttman-Yassky E, Blauvelt A, Eichenfield LF, Paller AS, Armstrong AW, Drew J, Gopalan R and Simpson EL: Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: A phase 2b randomized clinical trial. *JAMA Dermatol* 156: 411-420, 2020.
126. Hashimoto T, Yokozeki H, Karasuyama H and Satoh T: IL-31-generating network in atopic dermatitis comprising macrophages, basophils, thymic stromal lymphopoietin, and periostin. *J Allergy Clin Immunol* 151: 737-746.e6, 2023.
127. Kawai R, Ichimasu N and Katagiri K: IL-4 and IL-13 are not involved in IL-31-induced itch-associated scratching behaviour in mice. *Exp Dermatol* 33: e15115, 2024.
128. Girolomoni G, Maurelli M and Gisondi P: The emerging role of the neuroimmune cytokine interleukin-31 in chronic inflammatory skin diseases. *Ital J Dermatol Venereol* 157: 306-312, 2022.
129. Suehiro M, Numata T, Saito R, Yanagida N, Ishikawa C, Uchida K, Kawaguchi T, Yanase Y, Ishiujji Y, McGrath J and Tanaka A: Oncostatin M suppresses IL31RA expression in dorsal root ganglia and interleukin-31-induced itching. *Front Immunol* 14: 1251031, 2023.
130. Miron Y, Miller PE, Hughes C, Indersmitten T, Lerner EA and Cevikbas F: Mechanistic insights into the antipruritic effects of lebrikizumab, an anti-IL-13 mAb. *J Allergy Clin Immunol* 150: 690-700, 2022.
131. Xu J, Zanvit P, Hu L, Tseng PY, Liu N, Wang F, Liu O, Zhang D, Jin W, Guo N, *et al*: The cytokine TGF-β induces interleukin-31 expression from dermal dendritic cells to activate sensory neurons and stimulate wound itching. *Immunity* 53: 371-383.e5, 2020.
132. Imai Y: Interleukin-33 in atopic dermatitis. *J Dermatol Sci* 96: 2-7, 2019.
133. Trier AM, Mack MR, Fredman A, Tamari M, Ver Heul AM, Zhao Y, Guo CJ, Avraham O, Ford ZK, Oetjen LK, *et al*: IL-33 signaling in sensory neurons promotes dry skin itch. *J Allergy Clin Immunol* 149: 1473-1480.e6, 2022.
134. Bodoor K, Al-Qarqaz F, Heis LA, Alfaqih MA, Oweis AO, Almomani R and Obeidat MA: IL-33/13 axis and IL-4/31 axis play distinct roles in inflammatory process and itch in psoriasis and atopic dermatitis. *Clin Cosmet Investig Dermatol* 13: 419-424, 2020.

135. Kolkhir P, Pyatilova P, Ashry T, Jiao Q, Abad-Perez AT, Altrichter S, Vera Ayala CE, Church MK, He J, Lohse K, *et al*: Mast cells, cortistatin, and its receptor, MRGPRX2, are linked to the pathogenesis of chronic prurigo. *J Allergy Clin Immunol* 149: 1998-2009.e5, 2022.
136. Franke K, Wang Z, Zuberbier T and Babina M: Cytokines stimulated by IL-33 in human skin mast cells: Involvement of NF- κ B and p38 at distinct levels and potent Co-operation with Fc ϵ RI and MRGPRX2. *Int J Mol Sci* 22: 3580, 2021.
137. Tollenaere MAX, Hebsgaard J, Ewald DA, Lovato P, Garcet S, Li X, Pilger SD, Tiirikainen ML, Bertelsen M, Krueger JG and Norsgaard H: Signalling of multiple interleukin (IL)-17 family cytokines via IL-17 receptor a drives psoriasis-related inflammatory pathways. *Br J Dermatol* 185: 585-594, 2021.
138. Liu T, Li S, Ying S, Tang S, Ding Y, Li Y, Qiao J and Fang H: The IL-23/IL-17 pathway in inflammatory skin diseases: From bench to bedside. *Front Immunol* 11: 594735, 2020.
139. Lin W, Zhou Q, Liu C, Ying M and Xu S: Increased plasma IL-17, IL-31, and IL-33 levels in chronic spontaneous urticaria. *Sci Rep* 7: 17797, 2017.
140. Wang ZY, Zheng YX, Xu F, Cui YZ, Chen XY, Chen SQ, Yan BX, Zhou Y, Zheng M and Man XY: Epidermal keratinocyte-specific STAT3 deficiency aggravated atopic dermatitis-like skin inflammation in mice through TSLP upregulation. *Front Immunol* 14: 1273182, 2023.
141. Wang SH and Zuo YG: Thymic stromal lymphopoietin in cutaneous immune-mediated diseases. *Front Immunol* 12: 698522, 2021.
142. Yosipovitch G Berger T and Fassett MS: Neuroimmune interactions in chronic itch of atopic dermatitis. *J Eur Acad Dermatol Venereol* 34: 239-250, 2020.
143. Schaper-Gerhardt K, Rossbach K, Nikolouli E, Werfel T, Gutzmer R and Mommert S: The role of the histamine H₄ receptor in atopic dermatitis and psoriasis. *Br J Pharmacol* 177: 490-502, 2020.
144. Dai X, Muto J, Shiraishi K, Utsunomiya R, Mori H, Murakami M and Sayama K: TSLP impairs epidermal barrier integrity by stimulating the formation of nuclear IL-33/phosphorylated STAT3 complex in human keratinocytes. *J Invest Dermatol* 142: 2100-2108.e5, 2022.
145. Xia Q, Liu T, Wang J, Sun L, Chen X, Liu Y, Lu X, Liu H, Sun Y and Zhang F: Mast cells and thymic stromal lymphopoietin (TSLP) expression positively correlates with pruritus intensity in dermatitis herpetiformis. *Eur J Dermatol* 30: 499-504, 2020.
146. Hashimoto T, Nattkemper L, Kim H, Kursewicz CD, Fowler E, Shah SM, Nanda S, Fayne RA, Romanelli P and Yosipovitch G: Dermal periostin: A new player in itch of prurigo nodularis. *Acta Derm Venereol* 101: adv00375, 2021.
147. Hashimoto T, Kursewicz CD, Fayne RA, Nanda S, Shah SM, Nattkemper L, Yokozeki H and Yosipovitch G: Pathophysiologic mechanisms of itch in bullous pemphigoid. *J Am Acad Dermatol* 83: 53-62, 2020.
148. Hashimoto T, Mishra SK, Olivry T and Yosipovitch G: Periostin, an emerging player in itch sensation. *J Invest Dermatol* 141: 2338-2343, 2021.
149. Sari DW, Minematsu T, Yoshida M, Noguchi-Watanabe M, Tomida S, Kitamura A, Abe M and Sanada H: Validity of skin Blot examination for albumin and nerve growth factor β to detect itching of the skin in Indonesian older adults. *J Tissue Viability* 30: 42-50, 2021.
150. Wong LS, Lee CH and Yen YT: Increased epidermal nerve growth factor without small-fiber neuropathy in dermatomyositis. *Int J Mol Sci* 23: 9030, 2022.
151. Deng J, Parthasarathy V, Marani M, Bordeaux Z, Lee K, Trinh C, Cornman HL, Kambala A, Pritchard T, Chen S, *et al*: Extracellular matrix and dermal nerve growth factor dysregulation in prurigo nodularis compared to atopic dermatitis. *Front Med (Lausanne)* 9: 1022889, 2022.
152. Solinski HJ, Rukwied R and Schmelz M: Microinjection of pruritogens in NGF-sensitized human skin. *Sci Rep* 11: 21490, 2021.
153. Guseva D, Rüdrieh U, Kotnik N, Gehring M, Patsinakidis N, Agelopoulos K, Ständer S, Homey B, Kapp A, Gibbs BF, *et al*: Neuronal branching of sensory neurons is associated with BDNF-positive eosinophils in atopic dermatitis. *Clin Exp Allergy* 50: 577-584, 2020.
154. Zeng Q, Li Y, Wu Y, Wu J, Xu K, Chen Y, Rao Y, Li N, Luo Y, Jiang C, *et al*: Neuropeptide Y neurons mediate opioid-induced itch by disinhibiting GRP-GRPR microcircuits in the spinal cord. *Nat Commun* 16: 7074, 2025.
155. Wang Z, Jiang C, Yao H, Chen O, Rahman S, Gu Y, Zhao J, Huh Y and Ji RR: Central opioid receptors mediate morphine-induced itch and chronic itch via disinhibition. *Brain* 144: 665-681, 2021.
156. Yosipovitch G, Kim B, Luger T, Lerner E, Metz M, Adiri R, Canosa JM, Cha A and Ständer S: Similarities and differences in peripheral itch and pain pathways in atopic dermatitis. *J Allergy Clin Immunol* 153: 904-912, 2024.
157. Sheahan TD, Warwick CA, Cui AY, Baranger DAA, Perry VJ, Smith KM, Manalo AP, Nguyen EK, Koerber HR and Ross SE: Kappa opioids inhibit spinal output neurons to suppress itch. *Sci Adv* 10: eadp6038, 2024.
158. Kupczyk P, Hołysz M and Jagodziński PP: Opioid receptors in psoriatic skin: Relationship with itch. *Acta Derm Venereol* 97: 564-570, 2017.
159. Taneda K, Tominaga M, Negi O, Tengara S, Kamo A, Ogawa H and Takamori K: Evaluation of epidermal nerve density and opioid receptor levels in psoriatic itch. *Br J Dermatol* 165: 277-284, 2011.
160. Kim BS, Inan S, Ständer S, Sciascia T, Szepletowski JC and Yosipovitch G: Role of kappa-opioid and mu-opioid receptors in pruritus: Peripheral and central Itch circuits. *Exp Dermatol* 31: 1900-1907, 2022.
161. Bigliardi-Qi M, Lipp B, Sumanovski LT, Buechner SA and Bigliardi PL: Changes of epidermal mu-opiate receptor expression and nerve endings in chronic atopic dermatitis. *Dermatology* 210: 91-99, 2005.
162. Moniaga C, Iwamoto S, Kitamura T, Fujishiro M, Takahashi N, Kina K, Ogawa H, Tominaga M and Takamori K: Plasma dynorphin a concentration reflects the degree of pruritus in chronic liver disease: A preliminary report. *Acta Derm Venereol* 99: 442-443, 2019.
163. Kremer AE: Endogenous opioid levels do not correlate with itch intensity and therapeutic interventions in hepatic pruritus. *Front Med* 8: 641163, 2021.
164. Sun S, Xu Q, Guo C, Guan Y, Liu Q and Dong X: Leaky gate model: Intensity-dependent coding of pain and itch in the spinal cord. *Neuron* 93: 840-853, 2017.
165. Lay M and Dong X: Neural mechanisms of itch. *Annu Rev Neurosci* 43: 187-205, 2020.
166. Huang J, Polgár E, Solinski HJ, Mishra SK, Tseng PY, Iwagaki N, Boyle KA, Dickie AC, Kriegbaum MC, Wildner H, *et al*: Circuit dissection of the role of somatostatin in itch and pain. *Nat Neurosci* 21: 707-716, 2018.
167. Ross SE, Mardinly AR, McCord AE, Zurawski J, Cohen S, Jung C, Hu L, Mok SI, Shah A, Savner EM, *et al*: Loss of inhibitory interneurons in the dorsal spinal cord and elevated itch in Bhlhb5 mutant mice. *Neuron* 65: 886-898, 2010.
168. Acton D, Ren X, Di Costanzo S, Dalet A, Bourane S, Bertocchi I, Eva C and Goulding M: Spinal neuropeptide Y1 receptor-expressing neurons form an essential excitatory pathway for mechanical itch. *Cell Rep* 28: 625-639.e6, 2019.
169. Ren X, Liu S, Virlogeux A, Kang SJ, Brusch J, Liu Y, Dymecki SM, Han S, Goulding M and Acton D: Identification of an essential spinoparabrachial pathway for mechanical itch. *Neuron* 111: 1812-1829.e6, 2023.
170. Gao ZR, Chen WZ, Liu MZ, Chen XJ, Wan L, Zhang XY, Yuan L, Lin JK, Wang M, Zhou L, *et al*: Tac1-expressing neurons in the periaqueductal gray facilitate the itch-scratching cycle via descending regulation. *Neuron* 101: 45-59.e9, 2019.
171. Wang L, Peng J and Chen J: Case report: Dupilumab: A promising treatment option for adult linear IgA bullous dermatosis with severe pruritus. *Front Immunol* 15: 1409556, 2024.
172. Piyush Shah D and Barik A: The spino-parabrachial pathway for itch. *Front Neural Circuits* 16: 805831, 2022.
173. Dong X and Dong X: Peripheral and central mechanisms of itch. *Neuron* 98: 482-494, 2018.
174. Mu D, Deng J, Liu KF, Wu ZY, Shi YF, Guo WM, Mao QQ, Liu XJ, Li H and Sun YG: A central neural circuit for itch sensation. *Science* 357: 695-699, 2017.
175. Sanders XKM, Sakai K, Henry TD, Hashimoto XT and Akiyama XT: A subpopulation of amygdala neurons mediates the affective component of itch. *J Neurosci* 39: 3345-3356, 2019.
176. Su XY, Chen M, Yuan Y, Li Y, Guo SS, Luo HQ, Huang C, Sun W, Li Y, Zhu MX, *et al*: Central processing of itch in the midbrain reward center. *Neuron* 102: 858-872.e5, 2019.
177. Chen XJ, Liu YH, Xu NL and Sun YG: Itch perception is reflected by neuronal ignition in the primary somatosensory cortex. *Natl Sci Rev* 9: nwab218, 2022.
178. Zheng J, Zhang XM, Tang W, Li Y, Wang P, Jin J, Luo Z, Fang S, Yang S, Wei Z, *et al*: An insular cortical circuit required for itch sensation and aversion. *Curr Biol* 34: 1453-1468.e6, 2024.

179. Wu GY, Zheng XX, Zhao SL, Wang Y, Jiang S, Wang YS, Yi YL, Yao J, Wen HZ, Liu J, *et al*: The prelimbic cortex regulates itch processing by controlling attentional bias. *iScience* 26: 105829, 2023.
180. Zhang Z, Meng H and Li L: A preliminary study on traditional Chinese medicine in the development of senil antipruritic cosmetics. *J Light Industry* 32: 37-42, 2017 (In Chinese).
181. Ning Z, Yuxin Z, Yanan Z, Xiaohui Y, Guanru L and Fengjie Z: Systematic review and Meta-analysis of the clinical efficacy of oral Chinese medicine on pruritus. *World Chin Med* 16: 934-941, 2021.
182. Cristaudo A, Pigliacelli F, Sperati F, Orsini D, Cameli N, Morrone A and Mariano M: Instrumental evaluation of skin barrier function and clinical outcomes during dupilumab treatment for atopic dermatitis: An observational study. *Skin Res Technol* 27: 810-813, 2021.
183. Steinhoff M, Ahmad F, Pandey A, Datsi A, AlHammadi A, Al-Khawaga S, Al-Malki A, Meng J, Alam M and Buddenkotte J: Neuroimmune communication regulating pruritus in atopic dermatitis. *J Allergy Clin Immunol* 149: 1875-1898, 2022.
184. Tamari M and Ver Heul AM: Neuroimmune mechanisms of type 2 inflammation in the skin and lung. *Allergol Int* 74: 177-186, 2025.
185. Tominaga M and Takamori K: Peripheral itch sensitization in atopic dermatitis. *Allergol Int* 71: 265-277, 2022.
186. Torres T, Mendes-Bastos P, Cruz MJ, Duarte B, Filipe P, Lopes MJP and Gonçalo M: Interleukin-4 and atopic dermatitis: Why does it matter? A narrative review. *Dermatol Ther* 15: 579-597, 2025.
187. Biazus Soares G, Hashimoto T and Yosipovitch G: Atopic dermatitis itch: Scratching for an explanation. *J Invest Dermatol* 144: 978-988, 2024.
188. Garcovich S, Maurelli M, Gisondi P, Peris K, Yosipovitch G and Girolomoni G: Pruritus as a distinctive feature of type 2 inflammation. *Vaccines* 9: 303-318, 2021.
189. Wollenberg A and Giménez-Arnau A: Sensitive skin: A relevant syndrome, be aware. *J Eur Acad Dermatol Venereol* 36: 3-5, 2022.
190. Dong H, Peng M, Wang L, An Y and Miao M: Modern mechanisms and new advances in the treatment of external use of Chinese medicine in the treatment of chronic eczema. *China J Traditional Chin Med Pharmacy* 40: 4176-4180, 2025 (In Chinese).
191. Yue Y and Hou S: Research progress on pharmacological effects and clinical application of traditional Chinese medicine in treatment of chronic urticaria. *Chin Traditional Herbal Drugs* 53: 7596-7605, 2022 (In Chinese).
192. Liu L, Sun X, Mo M, Zhou Y, Li B, Zhang X and Li X: Clinical Diseases Responding Specially to TCM Treatment: Psoriasis. *Chin J Exp Traditional Med Formulae* 31: 260-268, 2025 (In Chinese).
193. Liu M, He B, Hu J, Dai Y, Ren L, Ge S, Li K, Jin Q, Song P and Chi H: Randomized Controlled Trials on Chinese Herbal Medicine Therapy for Atopic Dermatitis: An Evidence Map. *Chin J Exp Traditional Med Formulae* 31: 138-145, 2025 (In Chinese).
194. Xu Y, Guo Q, Chen Z, Liu Y and Yang Y: Overview of new indications for novel drugs approved in China between 2018 and 2024. *Drug Discovery Today* 30: 104342, 2025.
195. Tian S, Zhang J, Yuan S, Wang Q, Lv C, Wang J, Fang J, Fu L, Yang J, Zu X, *et al*: Exploring pharmacological active ingredients of traditional Chinese medicine by pharmacotranscriptomic map in ITCM. *Brief Bioinform* 24: bbad027, 2023.
196. Li K, Liu J, Wang T and Wu G: Rule of Prescriptions for Treatment of Pruritus by Modern Famous Chinese Medicine Based on Association Rule. *Liaoning J Traditional Chin Med* 50: 156-160, 2023 (In Chinese).
197. Zhang W, Cui N, Su F, Liu M, Li B, Sun Y, Zeng Y, Yang B, Kuang H and Wang Q: Effects of rehmanniae radix praeparata polysaccharides on LPS-induced immune activation in mice based on gut microbiota, metabolomics and transcriptomics. *Int J Biol Macromol* 311: 143981, 2025.
198. Zhang H, Wu ZM, Yang YP, Shaikat A, Yang J, Guo YF, Zhang T, Zhu XY, Qiu JX, Deng GZ and Shi DM: Erratum to: Catalpol ameliorates LPS-induced endometritis by inhibiting inflammation and TLR4/NF- κ B signaling. *J Zhejiang Univ Sci B* 21: 341-341, 2020.
199. Lu MK, Chang CC, Chao CH and Hsu YC: Structural changes, and anti-inflammatory, anti-cancer potential of polysaccharides from multiple processing of *Rehmannia glutinosa*. *Int J Biol Macromol* 206: 621-632, 2022.
200. Xin Q, Yuan R, Shi W, Zhu Z, Wang Y and Cong W: A review for the anti-inflammatory effects of paeoniflorin in inflammatory disorders. *Life Sci* 237: 116925, 2019.
201. Zhang L and Wei W: Anti-inflammatory and immunoregulatory effects of paeoniflorin and total glucosides of paeony. *Pharmacol Ther* 207: 107452, 2020.
202. Kong X and Dongmei S: The applications and mechanisms of paeoniflorin in dermatological disorders. *Chin J Dermatovenereol Integrated Traditional Western Med* 17: 473-476, 2018.
203. Chen J, He Q and Jin J: Targeting dendritic cell activation: The therapeutic impact of paeoniflorin in corticosteroid-dependent dermatitis management. *Arch Dermatol Res* 316: 348-359, 2024.
204. Chen L, Wang Y and Guan Z: Auxiliary effects of Heling emollient in children with mild atopic dermatitis. *Chin J Practical Pediatr* 38: 869-872, 2023 (In Chinese).
205. Ning J, Deng X, Chen L, Hang L, Zhu Y, Wu L, Xue Y and Yuan H: Construction and *in vitro* anti-inflammatory evaluation of a drug-loaded one-piece licorice exocyst-like particle-loaded licorice chalcone A nano-delivery system. *Acta Pharmaceutica Sinica* 60: 1147-1155, 2025 (In Chinese).
206. Shu J, Cui X, Liu X, Yu W, Zhang W, Huo X and Lu C: Licochalcone a inhibits IgE-mediated allergic reaction through PLC/ERK/STAT3 pathway. *Int J Immunopathol Pharmacol* 36: 3946320221135462, 2022.
207. Wang Y, Yang H, Chen L, Jafari M and Tang J: Network-based modeling of herb combinations in traditional Chinese medicine. *Briefings Bioinf* 22: bbab106, 2021.
208. Gao K, Liu L, Lei S, Li Z, Huo P, Wang Z, Dong L, Deng W, Bu D, Zeng X, *et al*: HERB 2.0: An updated database integrating clinical and experimental evidence for traditional Chinese medicine. *Nucleic Acids Res* 53: D1404-D1414, 2025.
209. Zhang Y, Li X, Shi Y, Chen T, Xu Z, Wang P, Yu M, Chen W, Li B, Jing Z, *et al*: ETCM v2.0: An update with comprehensive resource and rich annotations for traditional Chinese medicine. *Acta Pharm Sin B* 13: 2559-2571, 2023.
210. Li M, Ren Y, Lin Z, Liu L, Li Y, Li S, Guo R, Li P and Du B: Structural identification and anti-stomatitis activity of one arabinose-rich polysaccharide from *Rehmannia glutinosa*. *Int J Biol Macromol* 284: 138006, 2025.
211. Liu Y, Dong H, Sun-Waterhouse D, Li W, Zhang B, Yu J, Qiu Z and Zheng Z: Three anti-inflammatory polysaccharides from *Lonicera japonica* thunb: Insights into the structure-function relationships. *Food Sci Hum Wellness* 13: 2197-2207, 2024.
212. Bai X, Rao X, Wang Y, Shen H and Jin X: A homogeneous *Lonicera japonica* polysaccharide alleviates atopic dermatitis by promoting Nrf2 activation and NLRP3 inflammasome degradation via p62. *J Ethnopharmacol* 309: 116344, 2023.
213. Zhang T, Rao X, Song S, Tian K, Wang Y, Wang C, Bai X and Liu P: WLJP-025p, a homogeneous *Lonicera japonica* polysaccharide, attenuates atopic dermatitis by regulating the MAPK/NF κ B/AP-1 axis via Act1. *Int J Biol Macromol* 256: 128435, 2024.
214. Zhang H, Sun X, Qi H, Ma Q, Zhou Q, Wang W and Wang K: Pharmacological inhibition of the Temperature-sensitive and Ca²⁺-Permeable transient receptor potential vanilloid TRPV3 channel by natural forsythoside B attenuates pruritus and cytotoxicity of keratinocytes *J Pharmacol Exp Ther* 368: 21-31, 2019.
215. Guttman-Yassky E, Irvine AD, Brunner PM, Kim BS, Boguniewicz M, Parmentier J, Platt AM and Kabashima K: The role of Janus kinase signaling in the pathology of atopic dermatitis. *J Allergy Clin Immunol* 152: 1394-1404, 2023.
216. Shi HX, Gao YJ and Wang SR: Electroacupuncture in non-surgical management of lumbar spinal stenosis: Mechanistic potential in attenuating ligamentum flavum thickening via inflammatory factor modulation. *Front Immunol* 16: 1644394, 2025.
217. Yan J, Ye F, Ju Y, Wang D, Chen J, Zhang X, Yin Z, Wang C, Yang Y, Zhu C, *et al*: Cimifugin relieves pruritus in psoriasis by inhibiting TRPV4. *Cell Calcium* 97: 102429, 2021.
218. Zheng J, Gu A, Kong L, Lu W, Xia J, Hu H and Hong M: Cimifugin relieves histamine-independent itch in atopic dermatitis via targeting the CQ receptor MrgprA3. *ACS Omega* 9: 7239-7248, 2024.
219. Wang X, Wang Q, Zhang F and Wang J: The therapeutic effect of cimifugin on atopic dermatitis in mice and its mechanism. *Chin Pharmacological Bulletin* 12: 1648-1654, 2023 (In Chinese).
220. Yang N, Shao H, Deng J, Jin H, Xu L and Liu Y: Comparison and mechanism study on the anti-dermatitis effects of the main pharmacodynamic components of cortex dictamni including obacunone, dictamnine, and fraxinellone. *J Nanjing Med Univ* 43: 1636-1642, 1649, 2023 (In Chinese).

221. Wu D, Cao X and An Y: Syndrome Differentiation and Treatment of Psoriasis by Regulating Classical JAK/STAT Signaling Pathway with Traditional Chinese Medicine: A Review. *Chin J Exp Traditional Med Formulae* 29: 258-269, 2023 (In Chinese).
222. Yan S, Xindi Z and Hongying Z: Clinical study on Paeonol Ointment combined with tacrolimus in treatment of skin pruritus. *Drugs Clinic* 38: 1438-1441, 2023.
223. Hu Y, Zhou H, Huang Q and Yao Y: Effect of paeonol on the expression of cytokines production and maturation of DCs co-stimulated by FSL-1 and IL-4. *Chin J Clin Pharmacol Therapeutics* 24: 14-19, 2019 (In Chinese).
224. Wang D, Sun Z, Guo Q, Li X, Bai Y, Wei L and He Y: Therapeutic effect and mechanism of the topical preparation of baicalein atopical dermatitis. *J China Pharm Univ* 56: 99-109, 2025 (In Chinese).
225. Du LX, Gao XY, Ren XQ, Yang YY, Ding YY, Xu A, Wang XY, Zhang YX, Shu S, Yang YF, *et al*: Baicalein ameliorates chronic itch in ACD mice by suppressing the spinal astrocytic STAT3-LCN2 cascade. *Acta Pharmacol Sin* 46: 366-379, 2025.
226. Wang Y, Tan L, Jiao K, Xue C, Tang Q, Jiang S, Ren Y, Chen H, El-Aziz TMA, Abdelazeem KNM, *et al*: Scutellarein attenuates dermatitis by selectively inhibiting transient receptor potential vanilloid 3 channels. *Br J Pharmacol* 179: 4792-4808, 2022.
227. Um JY, Kim HB, Kim JC, Park JS, Lee SY, Chung BY, Park CW and Kim HO: TRPV3 and Itch: The role of TRPV3 in chronic pruritus according to clinical and experimental evidence. *Int J Mol Sci* 23L: 14962, 2022.
228. Lin Y, Chen XJ, He L, Yan XL, Li QR, Zhang X, He MH, Chang S, Tu B, Long QD and Zeng Z: Systematic elucidation of the bioactive alkaloids and potential mechanism from *sophora flavescens* for the treatment of eczema via network pharmacology. *J Ethnopharmacol* 301: 115799, 2023.
229. Luo Z, Zhao T, Yi M, Wang T, Zhang Z, Li W, Lin N, Liang S, Verkhatsky A and Nie H: The exploration of the potential mechanism of oxymatrine-mediated antipruritic effect based on network pharmacology and weighted gene co-expression network analysis. *Front Pharmacol* 13: 946602, 2022.
230. Kim M, Yuk HJ, Min Y, Kim DS and Sung YY: *Securinega suffruticosa* extract alleviates atopy-like lesions in NC/Nga mice via inhibition of the JAK1-STAT1/3 pathway. *Biomed Pharmacother* 169: 115903, 2023.
231. Park G, Kwon N, Kim MH and Yang WM: The slough of *cicadidae* periostacum ameliorated lichenification by inhibiting interleukin (IL)-22/janus kinase (JAK) 1/signal transducer and activator of transcription (STAT) 3 Pathway in atopical dermatitis. *Food Sci Anim Resour* 43: 859-876, 2023.
232. Neuberger A, Nadezhdin KD, Zakharian E and Sobolevsky AI: Structural mechanism of TRPV3 channel inhibition by the plant-derived coumarin osthole. *EMBO Rep* 22: e53233, 2021.
233. CallahanBN, KammalaAK, SyedM, YangC, OcchiutoCJ, NellutlaR, Chumanevich AP, Oskeritzian CA, Das R and Subramanian H: Osthole, a natural plant derivative inhibits MRGPRX2 induced mast cell responses. *Front Immunol* 11: 703, 2020.
234. Yang Q, Kong L, Huang W, Mohammadtursun N, Li X, Wang G and Wang L: Osthole attenuates ovalbumin-induced lung inflammation via the inhibition of IL-33/ST2 signaling in asthmatic mice. *Int J Mol Med* 46: 1389-1398, 2020.
235. Cheng Q, Zhuo Z, Duhua C, Ziyi L, Xuesong Y and Jianzhou Y: The role of transient receptor potential vanilloid 3 in the pathogenesis of atopical dermatitis. *Chin J Dermatovenereol* 1-11, 2025.
236. Wang W, Wang H, Zhao Z, Huang X, Xiong H and Mei Z: Thymol activates TRPM8-mediated Ca²⁺ influx for its antipruritic effects and alleviates inflammatory response in imiquimod-induced mice. *Toxicol Appl Pharmacol* 407: 115247, 2020.
237. Wang M, Luo H, Wei T, Lan C, Deng J and Jia J: Research progress on the physiological function and molecular mechanism of thymol. *China Feed* 13: 7-11, 2023 (In Chinese).
238. Jiang S, Zhang H, Li Y, Zhi W, Zong S and Liu Y: Research Progress on Pharmacological Effects of Sophocarpine Based on TLR4-NF- κ B/MAPK-Inflammatory Axis. *Chin Med J Res Prac* 37: 99-102, 2023 (In Chinese).
239. Yu D, Wang S, Fu Y, Yang L and Deng Z: Toxicity and Mechanism of Alkaloids in *Sophorae Tonkinensis Radix et Rhizoma*: A Review. *Chin J Exp Tradit Med Formulae* 28: 262-271, 2022 (In Chinese).
240. Zeng H, Zhang Z, Zhou D, Wang R, Verkhatsky A and Nie H: Investigation of the anti-inflammatory, anti-pruritic, and analgesic effects of sophocarpine inhibiting TRP channels in a mouse model of inflammatory itch and pain. *J Ethnopharmacol* 337: 118882, 2025.
241. Luo M, Zeng B, Wang H, Yang Z, Peng Y, Zhang Y and Wang C: *Kochia scoparia* saponin momordin ic modulates HaCaT cell proliferation and apoptosis via the wnt/ β -catenin pathway. *Evid Based Complement Alternat Med* 2021: 5522164, 2021.
242. Wang C, Jiao S, Zhou R, Huang P, Zeng B, Yang Z and Wang J: Momordin Ic ameliorates psoriasis skin damage in mice via the IL-23/IL-17 axis. *Arch Dermatol Res* 316: 474, 2024.
243. Lan J, Ma W and Chen L: Advances in researches on chemical constituents and pharmacological activities of *Kochia Scoparia*. *J Chin Med Materials* 47: 506-512, 2024 (In Chinese).
244. Yu H, Gachmaa B, Yu J, Liang T, Uranghai X, Guo G, Xu W, Wang P, Liu J, Jukov A, *et al*: A comprehensive and systemic review of the *Gentiana*: Ethnobotany, traditional applications, phytochemistry, pharmacology, and toxicology in the mongolian plateau. *J Ethnopharmacol* 345: 119573, 2025.
245. Zhao K, Pu S, Sun L and Zhou D: Gentiopicroside-loaded chitosan nanoparticles inhibit TNF- α -induced proliferation and inflammatory response in HaCaT keratinocytes and ameliorate imiquimod-induced dermatitis lesions in mice. *Int J Nanomed* 18: 3781-3800, 2023.
246. Qin C, Zhang S and Li Y: Study on Processing History, Chemical Composition and Pharmacological Effects of Longdan (*Gentiana Radix et Rhizoma*). *Chin Arch Traditional Chin Med* 44: 134-140, 2026 (In Chinese).
247. Gao Y, Ma R, Weng W, Zhang H, Wang Y, Guo R, Gu X, Yang Y, Yang F, Zhou A, *et al*: TRPV1 SUMOylation suppresses itch by inhibiting TRPV1 interaction with H1 receptors. *Cell Rep* 39: 110972, 2022.
248. Song Y, Zheng W and Hua Z: Effect mechanism of *Tripterygium wilfordii* in treatment of psoriasis based on network pharmacology and molecular docking. *Chemistry Life* 42: 1188-1200, 2022 (In Chinese).
249. Song Y, Ding Q, Hao Y, Cui B, Ding C and Gao F: Pharmacological effects of shikonin and its potential in skin repair: A review. *Molecules* 28: 7950, 2023.
250. Mu Z, Guo J, Zhang D, Xu Y, Zhou M, Guo Y, Hou Y, Gao X, Han X and Geng L: Therapeutic effects of shikonin on skin diseases: A review. *Am J Chin Med* 49: 1871-1895, 2021.
251. Liang J, Chen W, Zhou Y, Meng W, Xie M, Weng Y, Qin L, Li J and Wu G: Inhibitory effect of evodiamine on psoriasis lesions and itching in mice. *Clin Cosmet Investig Dermatol* 17: 1527-1541, 2024.
252. Hu M, Liu Q, Zang X, Hu J, Du J and Zhou W: Effect of Rutaecarpine on Imiquimod (IMQ)-induced Psoriasis-like Mouse Model. *Chin J Dermatovenereol* 34: 1366-1371, 2020 (In Chinese).
253. Wei Q, Jin Q, Jin L, Yu R, Li F, Li H, Jin D, Meng F and Jin G: Dihydroartemisinin alleviates psoriasis-like skin inflammation in mice by inhibiting proliferation of keratinocytes and expression of pro-inflammatory cytokines. *Chin J Immunol* 36: 543-548, 2020 (In Chinese).
254. Yang J, Wang R, Wang R and Zhang S: Preparation of dihydroartemisinin-loaded liposomes and their topical efficacy in alleviating psoriasis-like lesions in mice. *Drug Evaluation Res* 48: 1853-1868, 2025 (In Chinese).
255. Cui HR, Zhang JY, Cheng XH, Zheng JX, Zhang Q, Zheng R, You LZ, Han DR and Shang HC: Immunometabolism at the service of traditional chinese medicine. *Pharmacol Res* 176: 106081, 2022.
256. Wang X, Shi X, Xi Z, Zhang Z, Luo Z, Wang J and Shan J: The scientific basis of synergy in traditional chinese medicine: Physicochemical, pharmacokinetic, and pharmacodynamic perspectives. *Chin Med* 21: 15-35, 2026.
257. Yang X, Luo Y and Ding C: MRHAF: Multi-relational hierarchical attention with hybrid knowledge fusion for explainable herb recommendations. *IEEE J Biomed Health Inform*: December 15, 2025 (Epub ahead of print).
258. Si F and Zhao Z: Distribution of TCM syndromes and prescription rules of skin pruritus. *Traditi Chin Med Res* 34: 39-42, 2021 (In Chinese).
259. Liu XY, Zheng HW, Wang FZ, Atia TW, Fan B and Wang Q: Developments in the study of chinese herbal medicine's assessment index and action mechanism for diabetes mellitus. *Anim Models Exp Med* 7: 433-443, 2024.
260. Cui J, May BH, Lin W, Luo Q, Zhang AL, Guo X, Lu C, Li Y and Xue CC: Chinese herbal medicines for rhinosinusitis: A text-mining study with comparisons to contemporary research and clinical guidance. *BMC Complement Med Ther* 25: 165, 2025.
261. Li C, Jia W, Yang J, Cheng C and Olaleye OE: Multi-compound and drug-combination pharmacokinetic research on Chinese herbal medicines. *Acta Pharmacol Sin* 43: 3080-3095, 2022.

262. Li HH, Livneh H, Huang HL, Wang YH, Lu MC, Chen WJ and Tsai TY: Integrating Chinese herbal medicine into conventional care was related to lower risk of sarcopenia among rheumatoid arthritis patients: A retrospective, population-based study. *J Multidiscip Healthc* 39: 411-415, 2025 (In Chinese).
263. Wang S, Ma Y, Cui Z and Diao J: A case of factitious disorders as Henoch-Schonlein purpura. *Chin Mental Health J* 39: 411-415, 2025 (In Chinese).
264. Zhang M, Xue P, Zhao Y, Gao Y, Dong W, Ma W, Wang Z and Zhang C: Protective Effect of Longdan Xiegan Decoction on Eczema Rats Regulating H1R/TRPV1, PAR-2/TRPV1 and P38MAPK Signal Pathway. *World Sci Technol Modernization Traditi Chin Med* 24: 2331-2339, 2022 (In Chinese).
265. Ni Z, Cheng-Yan W, Qing-Wu S and Zi-He W: Textual research on the classical prescription danggui decoction. *Modern Chin Med* 25: 888-899, 2023.
266. Zhang X, Wei Q, Cai C, Pang Y, He Y, Wu S, Guo J and Zeng J: Effect of Danggui Yinzi on Relieving Allergic Reactions in UL Mice by Inhibiting IL-33-mediated Degranulation of Mast Cells. *Chin Arch Traditional Chin Med* 39: 144-148, 268-270, 2021 (In Chinese).
267. Yao B, Wang J and Ran Z: Effect and Mechanism of Danggui Yinzi on Eczema Model of Blood Deficiency and Wind Dryness. *World Sci Technol Modernization Traditi Chin Med* 24: 4055-4062, 2022.
268. Li P, Yu Q, Nie H, Yin C and Liu B: IL-33/ST2 signaling in pain and itch: Cellular and molecular mechanisms and therapeutic potentials. *Biomed Pharmacother* 165: 115143, 2023.
269. Wu S and Lan C: Clinical study on the efficacy and safety of liangxue xiaofeng san combined with levocetirizine oral solution in treating chronic spontaneous urticaria with blood-heat and wind-generation pattern in Children. *Lishizhen Med Materia Med Res* 34: 2168-2171, 2023 (In Chinese).
270. Li'Na F, Yige W, Yi H, Ke X, Jin H, Shijiao S and Guang Z: Study on regulation mechanism of xiaofeng powder for damp-heat accumulation skin type epidermal barriers. *J Sichuan Traditi Chin Med* 39: 43-48, 2021.
271. Roh YS, Choi J, Sutaria N, Belzberg M, Kwatra MM and Kwatra SG: IL-31 inhibition as a therapeutic approach for the management of chronic pruritic dermatoses. *Drugs* 81: 895-905, 2021.
272. Huang IH, Chung WH, Wu PC and Chen CB: JAK-STAT signaling pathway in the pathogenesis of atopic dermatitis: An updated review. *Front Immunol* 13: 1068260, 2022.
273. Kim SY, Han SD, Kim M, Mony TJ, Lee ES, Kim KM, Choi SH, Hong SH, Choi JW and Park SJ: *Mentha arvensis* essential oil exerts anti-inflammatory in LPS-stimulated inflammatory responses via inhibition of ERK/NF- κ B signaling pathway and anti-atopic dermatitis-like effects in 2,4-dinitrochlorobenzene-induced BALB/c mice. *Antioxidants (Basel)* 10: 1941, 2021.
274. Fu B, Ji Y, Li J, Pei M and Yang H: Network Pharmacology-based Mechanism of *Guizhi Mahuang Geban* Decoction in the Treatment of Uraemic Pruritus. *New Chinese Med and Clin Pharmacology* 32: 1675-1684, 2021 (In Chinese).
275. Niu F, Li B, Wang S, Li Y and Zhou W: Taohong Siwangtang Exerts Anti-inflammatory Effect and Regulates Caspase-14 and EVPL Expression in Treatment of Psoriasis. *Chin J Exp Traditi Med Formulae* 24: 12-21, 2024 (In Chinese).
276. Zhang Z, Zhang H, Guan J and Chen Y: Study on the Effect and Mechanism of Huanglian Jiedu Decoction in Improving Itching Symptoms in 1-chloro-2,4-dinitrobenzene-Induced Atopic Dermatitis Mice. *Traditi Chin Drug Res Clin Pharmacol* 6: 1713-1720, 2023 (In Chinese).
277. Li D, Xing Y and Wang B: Pharmacological Mechanism of Huanglian Jiedutang: A Review. *Chin J Exp Traditi Med Formulae* 24: 275-283, 2025 (In Chinese).
278. Long S, Wen C, Zhu H, Wang Y, Li H and Wu X: Effects of modified guominjian decoction on degranulation of mast cells in larva of urticaria model mice. *J Traditi Chin Med* 60: 322-326, 2019 (In Chinese).
279. Gao J, Chen G, Tan W, Lan J, Zhang J, Rao G, Wang R and Zhang Y: Interventional effects of Guo Min Jian (Anti-Allergy Decoction) on atopic dermatitis in a murine model. *Lishizhen Med Materia Med Res* 33: 1806-1810, 2022 (In Chinese).
280. Juan G, Guifang C, Wei T, Jie Z, Gaoxiong R, Ruirui W and Yi Z: Mechanism of guomin decoction to improve atopic dermatitis by inhibiting mast cell degranulation through IgE/Fc ϵ RI pathway. *Chin Arch Traditi Chin Med* 42: 135-140, 283-284, 2024.
281. Huang J, Xu Y, Yang X, Wang J, Zhu Y and Wu X: Jiawei guomin decoction regulates the degranulation of mast cells in atopic dermatitis mice via the HIS/PAR-2 pathway. *J Ethnopharmacol* 321: 117485, 2024.
282. Tan W, Liu Y, Deng S, Wang R, Rao G, Zhang L and Zhang Y: Preliminary mechanism study on the antipruritic effect of Danggui Kushen Pill. *Chin J Hosp Pharmacy* 43: 1786-1794, 2023 (In Chinese).
283. Xing C, Mei W, Lixia H, Xinhong L, Qiuying W and Jing T: Mechanism of Danggui Kushen pill in treating eczema based on network pharmacology. *J Shenyang Pharmaceutical Univ* 38: 845-854, 2021.
284. Gu Q, Lin J, Lu X, Chen T, Wu Y and Yang Y: Jiu-Wei-Yong-An formula suppresses JAK1/STAT3 and MAPK signaling alleviates atopic dermatitis-like skin lesions. *J Ethnopharmacol* 295: 115428, 2022.
285. Yu H, Zhang W, Rao Q and Zhou M: *Yupingfeng* Granules Relieving Pruritus via Inhibiting Mast Cells and IL-31 in Atopic Dermatitis Rats. *New Drugs Clin Pharmacology Trad Chin Med* 33: 1017-1024, 2022 (In Chinese).
286. Wen W, Zhang H, Lin M, Yu C, Xu E and Xu J: Effects of Yupingfeng Powder Combined with Desloratadine on Serum Inflammatory Factors and Quality of Life in Children with Chronic Urticaria. *Med Innovation China* 19: 78-81, 2022.
287. Wang J, Chen Y, Yang X, Huang J, Xu Y, Wei W and Wu X: Efficacy and safety of Chinese herbal medicine in the treatment of chronic pruritus: A systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol* 13: 1029949, 2023.
288. Ferrannini E and Rosenstock J: Clinical translation of cardiovascular outcome trials in type 2 diabetes: Is there more or is there less than meets the eye? *Diabetes Care* 44: 641-646, 2021.
289. Zhang Y and Chow SC: Mapping of subjective measurements in traditional Chinese medicine to objective clinical endpoints in western medicine. *Biologics* 18: 433-452, 2024.
290. Liu Y, Xu J, Yu Z, Chen T, Wang N, Du X, Wang P, Zhou X, Xu H and Zhang Y: Ontology characterization, enrichment analysis, and similarity calculation-based evaluation of disease-syndrome-formula associations by applying SoFDA. *Imeta* 2: e80, 2023.
291. Lin YH, Sahker E, Shinohara K, Horinouchi N, Ito M, Lelliott M, Cipriani A, Tomlinson A, Baethge C and Furukawa TA: Assessment of blinding in randomized controlled trials of antidepressants for depressive disorders 2000-2020: A systematic review and meta-analysis. *EclinicalMedicine* 50: 101505, 2022.
292. Ren Y, Jia Y, Yang M, Yao M, Wang Y, Mei F, Li Q, Li L, Li G, Huang Y, *et al*: Sample size calculations for randomized controlled trials with repeatedly measured continuous variables as primary outcomes need improvements: A cross-sectional study. *J Clin Epidemiol* 166: 111235, 2024.
293. Llovera G, Langhauser F, Isla Cainzos S, Hoppen M, Abberger H, Mohamad Yusuf A, Mencl S, Heindl S, Ricci A, Hauptelshofer S, *et al*: Stroke of consistency: Streamlining multicenter protocols for enhanced reproducibility of infarct volumes in preclinical stroke research. *Stroke* 55: 2522-2527, 2024.
294. Day J, Antony A, Tillett W and Coates LC: The state of the art-psoriatic arthritis outcome assessment in clinical trials and daily practice. *Lancet Rheumatol* 4: e220-e228, 2022.
295. Leung AYL, Zhang J, Chan CY, Chen X, Mao J, Jia Z, Li X and Shen J: Validation of evidence-based questionnaire for TCM syndrome differentiation of heart failure and evaluation of expert consensus. *Chin Med* 18: 70, 2023.



Copyright © 2026 Zhang et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.