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Review

Itching in skin allergic diseases: Dermocosmetics between diagnostic work-up and innovative or emerging drugs. Review on proper advice and prescription

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Abstract. *Introduction:* Itch or pruritus is "an unpleasant sensation that evokes the desire to scratch"; it is defined as "chronic" if it persists for more than six weeks. Many authors include chronic itching among allergic-immunological disorders. Chronic spontaneous urticaria, atopic dermatitis, allergic contact dermatitis, and prurigo nodularis are some of the allergic diseases characterized by itch. This symptom, as well as being histaminergic, can be supported by specific sensory neuronal circuits and by inflammatory mediators, epithelial and effector cytokines, and other molecules which, through distinct, interdependent or synergistic pathways, are involved in chronic itching. *Objectives:* This work aims to provide an updated consultation and review of the literature regarding pruritus, in both diagnostic and therapeutic contexts. It also aims to evaluate the role of topical and active cosmetic ingredients in soothing itch and repairing the barrier damage responsible for it. *Methods:* A review of available literature (PubMed, various search terms) was conducted. Indications and guidelines were analyzed regarding topical ingredients considered effective in addressing itch and skin barrier repair. *Results:* A diagnostic-therapeutic algorithm is proposed, based on recent findings on the biology of pruritus and targeted therapies. The rationale for a dermocosmetic prescription is identified as an alternative, complementary, or synergistic therapeutic option alongside traditional or innovative drugs. *Conclusions:* Recent insights into the biology of pruritus, a debilitating symptom in many allergic diseases, have led to the development of precise diagnostic-therapeutic algorithms. While new molecules and targeted drugs are being explored, hydrating topicals have been shown to alleviate symptoms, improve skin barrier function, and reduce allergen penetration and bacterial contamination.

Introduction

Pruritus is an uncomfortable sensation leading to a scratch response, evolutionarily conserved to expel noxious environmental substances in its acute form.

Chronic pruritus is defined as itch lasting greater than 6 weeks, resulting from several underlying etiologies, including inflammatory skin conditions, malignancies, chronic kidney and hepatobiliary disease, endocrine, neuropathic and psychogenic disorders.

Chronic itching of unknown origin is restrictive on the health-related quality-of-life for patients, and a diagnostic and therapeutic challenge for clinicians. Despite limited efficacious treatments, the understanding

of novel itch-sensory pathways has lead to the development of new, targeted therapies. This paper aims to underline the importance of correct cleansing and protection of the skin barrier in allergic skin diseases characterized by chronic pruritus. Based on data in the literature, a list of topical ingredients providing relief from symptoms, improving the functionality of the skin barrier, and reducing the penetration of allergens and bacterial contamination is provided.

Biology of itching in allergic skin diseases

Histaminergic itch, typical of acute urticaria, is a feature of type I hypersensitivity. Mast cells release histamine after IgE-mediated activation through its cell-surface high-affinity receptor, FcεRI. Degranulation occurs near itch-sensory nerve fibers in the skin, pruritogens are released and bind their respective receptors on terminal axons. This triggers the opening of non-specific cation channels, such as transient receptor potential A1 (TRPA1), transient receptor potential V1 (TRPV1), or both, resulting in membrane depolarization and subsequent activation of an action potential by voltage-gated ion channels, NaV1.7 and NaV1.8. Itch-sensory signals are relayed through unmyelinated and slow-conducting C-fibers to their respective cell bodies in the dorsal root ganglia and subsequently transmitted to the dorsal horn of the spinal cord in the central nervous system and ultimately to the brain, where these signals are perceived as an itchy sensation[1]. In other allergic, immunologic, and systemic diseases, pruritus is mediated by non-histaminergic pruritogens, including tryptase, substance P, interleukins (IL)-1, -4, -13, and -31, thymic stromal lymphopoietin (TSLP), eosinophil cationic protein, major basic protein, and superoxide anion (O_2^-). These factors act either through direct activation of epidermal nerve fibers by external mechanical, chemical, or physical stimuli, or via modulation of opioid pathways and histamine H4 receptors[2]. The gastrin-releasing peptide receptor[3], Mas-related G protein–coupled receptor (Mrgpr) family[4,5], natriuretic peptide B (Nppb)[6,7], and various itch-mediating cytokine receptors, represent new and emerging pathways to be considered and targeted for the treatment. Pruritogens induce itching mainly by acting on the sensory nerves, causing one to scratch the affected area, further aggravating skin discomfort. This vicious cycle is called the "itch-scratch cycle"[8]. The somatosensory sensation of itch, especially chronic itch, is closely associated with dry skin, either as a clinical manifestation of dermatoses such as xerosis, atopic dermatitis (AD), and psoriasis, or of a common cutaneous manifestation in pruritic systemic diseases, such as chronic kidney disease (CKD), chronic liver diseases (CLD), and diabetes mellitus (DM)[9]. Thus, aged skin, inflammatory skin diseases, and cutaneous xerosis connected to systemic diseases, could be among the underlying conditions impairing skin barrier functions such as trans epidermal water loss (TEWL), stratum corneum (SC) hydration, and pH[10].

Histaminergic itch mechanisms are briefly illustrated in Figure 1.

Non-histaminergic itch mechanisms are briefly illustrated in Figure 2.

Classification of pruritus and diagnostic work up

The International Forum for the study of itch (IFSI) developed a classification of chronic pruritus in 2007, which is still considered correct. Three groups of conditions are proposed: pruritus on inflamed skin (group I), pruritus on non-inflamed skin (group II),

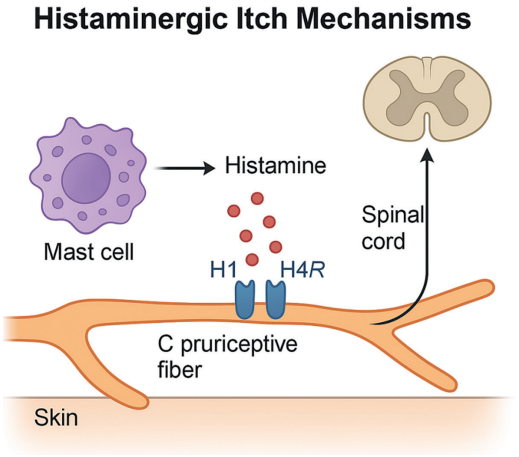

Figure 1. Figure created by the author with the aid of AI-based illustration tools.

and pruritus presenting with severe chronic secondary scratch lesions, such as prurigo nodularis (group III). Underlying diseases are classified: dermatological, systemic - including diseases of pregnancy and drug-induced pruritus - neurological and psychiatric.

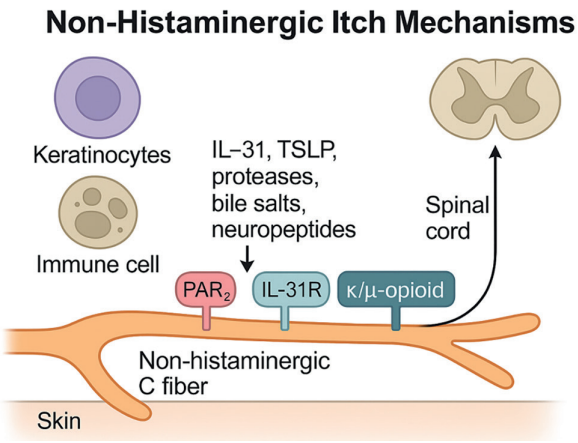

Figure 2. Figure created by the author with the aid of AI-based illustration tools.

In some patients more than one cause may account for pruritus ("mixed") while in others, no underlying disease can be identified ("others")[11]. Given their imprecise definitions, historical terms such as pruritus *sine materia*, senile pruritus, psychogenic pruritus, should be avoided[12].

Clinically, pruritus can be divided into six types: itch caused by systemic diseases, caused by skin diseases, neuropathic pruritus, psychogenic pruritus, pruritus with multiple factors, and from unknown causes[11] (Table 1).

A primary skin lesion should be sought or skin changes secondary to scratching should be characterized. When the cause is not dermatological, routine laboratory tests are carried out, as well as serology for HIV, hepatitis viruses, heavy metal exposure, hypovitaminosis, parasitosis.

In the case of suspected occult neoplasia, especially hepatobiliary and hematological malignancies, further radiological and laboratory investigations such

Table 1. Itch classification (IFSI modified)[13].

IFSI groups	Clinical presentation	Etiology	Examples
Group I	Inflamed, diseased- skin	Dermatologic	Atopic dermatitis Psoriasis Allergic contact dermatitis Lichen planus
Group II	Non-inflamed, non- diseased skin	Systemic	Cholestatic itch Uremic itch Paraneoplastic itch Diabetes-associated itch
Group III	Secondary lesions from chronic scratching, rubbing, picking	Neuropathic	Scalp dysesthesia Brachioradial pruritus Notalgia paresthetica Anogenital pruritus
		Psychogenic	Delusion of parasitosis Excoriation disorder Morgellon disease Substance use disorder
Mixed: more than one cause may account for pruritus			
Other: no underlying disease can be identified			
I diagnostic step: clinical picture only			
II diagnostic step: histological, laboratory, radiological investigation			

General approach to itch based on clinical presentation and underlying etiology. These are not absolute categories but represent a general scheme.

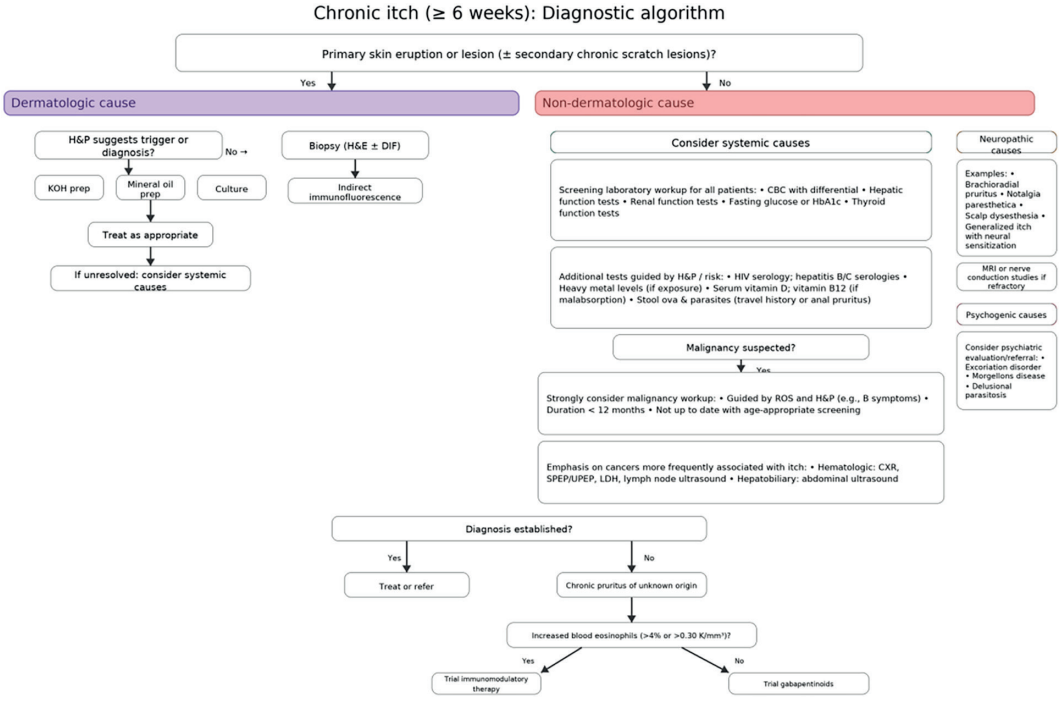

Figure 3. Diagnostic workup algorithm of chronic itch[14-20]. CBC: Complete blood count; CXR: chest x-ray; DIF: direct immunofluorescence; Dx: diagnosis; H&E: hematoxylin and eosin; H&P: history and physical examination; HbA1c: hemoglobin A1c; KOH: potassium hydroxide; LDH: lactate dehydrogenase; MRI: magnetic resonance imaging; ROS: review of systems; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis. Figure created by the author with the aid of AI-based illustration tools, based on data and concepts from the scientific literature.

as chest X-ray, serum or urine electrophoresis and ultrasonography are recommended.

Finally, neuropathic and psychogenic causes should not be overlooked. If a possible systemic etiology is not identified, the patient will be given the diagnosis of chronic pruritus of unknown origin (CPUO), which should be correlated with blood eosinophil levels (Figure 3).

Pruritus in skin allergic diseases

Many authors include chronic itch, both histaminergic and nonhistaminergic, among allergic and immunologic disorders.

Itch in chronic spontaneous urticaria

Urticaria is characterized by pruritic wheals or hives on the skin that typically last for 24 hours or less and often migrate. The causes can be numerous, including allergic reactions, mechanical stimulation, autoimmunity, or simply idiopathic. In the setting of acute urticaria, it is well understood that the activation of IgE by putative antigens results in the activation of mast cells (and basophils) and the release of preformed mediators, the most important being histamine. This process results in the elicitation of hives and associated histaminergic pruritus that is often responsive to antihistamines. However, when urticaria is chronic and occurs for a period greater than 6 weeks, it is described as chronic spontaneous urticaria (CSU), and its associated chronic itch becomes more difficult to manage, suggesting the involvement of a histamine-independent pathway mediating itch[1].

Mechanisms of chronic itch in CSU are resumed in Table 2.

Table 2. Pathophysiology of itch in CSU.

- In acute urticaria, antigens activating IgE induce mast cells and basophils to release preformed mediators, the most important being histamine, with consequent elicitation of hives and associated histaminergic itch (often responsive to antihistamines).
- Mast cells synthesize and release histamine and other mediators: eicosanoids, such as prostaglandin D2 and leukotriene C4, D4, and E4[21].
- Well-recognized immunologic stimuli can degranulate mast cells through the IgE receptor, including IgG antibodies to IgE (5% to 10% of patients) or FcεRI (30% to 40% of patients) in the context of CSU[22].
- Other cell types have been implicated, as evidenced by the presence of eosinophils, neutrophils, and lymphocytes in urticarial skin lesions on histology[23].
- Histamine receptor 1 and histamine receptor 4 (H4R) on sensory neurons have been implicated in itch[24,25].
- H4R expressed on mast cells indicates additional indirect mechanisms of mast cells' stimulation to release pruritogens. H4 antagonist demonstrated significant reduction in histamine-induced pruritus with no effect on wheal formation[26].
- Mrgprb2 is a key receptor that mediates IgE-independent mast cell activation, thus urticarial itch[27-29].

Itch in atopic dermatitis

Atopic dermatitis (AD) is a common chronic and relapsing inflammatory skin disorder characterized by intense pruritus and scaly red rashes involving classic locations (cheeks and extensor extremities in infants and flexural sites in children and adults). It typically presents during infancy and can persist into adulthood[30]. In contrast to urticaria, it is well established now that AD-associated pruritus is largely nonhistaminergic in nature. Indeed, several cytokines, mostly those associated with the type 2 immune response (e.g. IL-4, IL-13, IL-31, IL-33 and TSLP), have been implicated in mediating both inflammation and neurophysiologic pruritus in the context of AD. Recent advances in our understanding of the neuroimmune basis of AD-associated itch have emboldened the development of new treatments for AD and provoked the hypothesis that other immunologically related disorders might also be amenable to similar therapeutic interventions[1].

Mechanisms of itch in AD are resumed in Table 3.

Table 3. Pathophysiology of itch in AD.

- AD is associated with enhanced mast cell activation and histamine release: the effects of H4 antihistamines for the treatment of AD and its resulting itch are currently under investigation.
- IL-31, produced by TH2 cells in the context of AD, is the first cytokine identified as a pruritogen[31].
- Nemolizumab, an anti–IL-31 receptor (IL-31 receptor A) blocking mAb, has demonstrated antipruritic efficacy in patients with AD[32].
- TSLP and IL-33, epithelial cell–derived cytokines of type 2 cellular responses directly stimulate itch-sensory neurons in vivo[33,34].
- Anti-TSLP (Tezepelumab) and anti–IL-33 (Etokimab) mAbs are being explored in clinical trials for AD[35].
- Dupilumab was the first US Food and Drug Administration (FDA)–approved mAb for the treatment of AD and targets IL-4 receptor A to block both IL-4 and IL-13 signaling[36].
- Anti–IL-13 mAbs Tralokinumab and Lebrikizumab significantly improve AD-associated itch[37,38].
- Lymphocytic AD-associated cytokines are dependent on Janus kinase (JAK)–signal transducer and activator of transcription signaling for their effects on cellular transcription and activation[39].
- Topical Tofacitinib (JAK1/3 inhibitor), JTE-052 (pan-JAK inhibitor), and Ruxolitinib (JAK1/2 inhibitor) have rapid effects on the resolution of itch[40-43].
- JAK inhibitors likely have neuromodulatory properties[44].
- Oral JAK1-selective inhibitors Upadacitinib for the treatment of AD demonstrates potent anti-itch effects as well[45].
- Baricitinib, a JAK1/2 inhibitor, was also able to improve AD rash in addition to AD-associated pruritus in a phase 2 trial[46].

Itch in prurigo nodularis

Prurigo nodularis (PN) is classically characterized as a neurodermatosis: the underlying itch drives the development of the rash, typically characterized by multiple dome-shaped hyperkeratotic nodules. Lesions are symmetrically distributed on the extensor surfaces of the extremities and on areas of the torso accessible to scratching, with the mid-back commonly spared; the flexural surfaces, palms, soles, face, and groin are rarely affected. Intense pruritus and chronic repetitive scratching, rubbing, or picking are observed[47].

PN presents in the context of several systemic diseases, including chronic kidney disease and HIV, but can also manifest independently[48-50]. Strikingly, 50%

of patients with PN exhibit atopy as a comorbid entity. Although exhibiting distinct clinical features, even in the context of AD, PN has demonstrated similar pathologic features to AD. Thus, it is likely that PN will respond to drugs currently explored or used in the setting of AD.

Mechanisms of pruritus in PN are resumed in Table 4.

Chronic pruritus of unknown origin

Chronic pruritus of unknown origin (CPUO) presents as generalized pruritus with no clearly defined cause. These patients typically do not exhibit a rash but are widely believed to have a type 2 immune profile[59]. Increased eosinophils in the dermis and in the blood, and mild increases in serum IgE levels are common[60]. Additionally, the transcriptional profiling of CPUO skin demonstrated a distinct but similar profile to lesional AD skin[61]. However, unlike atopic dermatitis (AD), patients with chronic pruritus of unknown origin (CPUO), while exhibiting a type 2 immune profile, are thought to have milder systemic inflammation and generally lack a history of atopic disease. No FDA-approved medications exist for the treatment of CPUO[1].

Mechanisms of pruritus in CPUO are resumed in Table 5.

Itch in allergic contact dermatitis

Allergic contact dermatitis (ACD) is an itchy eczematous reaction of the skin that occurs hours to days after encountering an allergen. Unlike irritant contact dermatitis, which results from an irritant chemical causing a direct toxic effect on the skin, ACD is a delayed type IV hypersensitivity reaction to a hapten or antigen[65]. Although irritant contact dermatitis and ACD are often difficult to distinguish from each other,

Table 4. Pathophysiology of itch in PN.

- PN and AD share common pathologic features: both PN and AD are associated with histologic features of hyperkeratosis and a mixed dermal inflammatory infiltrate (lymphocytes, neutrophils, mast cells, and occasional eosinophils)[51].
- AD and PN are associated with increased expression of IL-31 within the lesions[52].
- Both patients with AD and PN have lesions with increased density of nerve fibers innervating the skin[53,54].
- Dupilumab demonstrated clinically meaningful and statistically significant improvements in itch and skin lesions versus placebo in PN, in a recent phase III trial[55].
- Nemolizumab monotherapy significantly reduced the signs and symptoms of prurigo nodularis in a recent phase III trial[56].
- Vixarelimab, a human monoclonal antibody binding to the beta subunit of the oncostatin M receptor, inhibiting signaling of both IL-31 and oncostatin M, led to a relief of itch and clearing of skin nodules in patients suffering from PN[57].
- Neurokinin 1 receptor antagonist Serlopitant reduces pruritus intensity in PN[58].

Table 5. Pathophysiology of itch in CPUO.

- Patients with CPUO could have sensory neuronal dysfunction that potentiates the effects of type 2 inflammation to drive itch[61].
- CPUO has been associated with pruritus in elderly patients[62].
- Current guidelines recommend the use of several therapy options, including emollients, antihistamines, gabapentinoids and antidepressants, for the treatment of CPUO[63].
- Patients with CPUO responded to systemic Tofacitinib[64].

Table 6. Pathophysiology of itch in ACD.

- The precise mechanisms underlying itch in patients with ACD remain poorly defined.
- Recent studies are demonstrating novel T cell–independent mechanisms as key players in ACD-associated itch.
- Epithelial cell–derived IL-33 can directly stimulate itch-sensory neurons in a murine model of ACD[33].
- Mast cells have been implicated in modulating ACD-associated inflammation[68].
- Proadrenomedullin peptide, an endogenous activator of Mrgprb2/X2, is critically upregulated in lesional human ACD skin. Its activity is entirely independent of histamine[1].
- Mrgprb2-elicited activation resulted in smaller amounts of histamine release but greater release of tryptase[69].
- Chemogenetic activation of mast cells results in the release of serotonin, leukotriene C4, and sphingosine-1-phosphate. Nppb neurons express receptors for these molecules, which activate itch along the gastrin-releasing peptide–spinal cord pathway[70].

patch testing is the gold standard test to determine culprit allergens that favor a diagnosis of ACD. Like many other chronic itch disorders, histamine is poorly involved in ACD.

Mechanisms of itch in ACD are resumed in Table 6.

Traditional drugs for chronic pruritus

Underlying cause of pruritus needs to be identified and treated although etiological treatment is not always sufficient to improve it, and pruritus frequently remains of unknown origin and a therapeutic challenge.

Traditional topical treatments for itching are summarized in Table 7.

Traditional systemic treatments for itching are summarized in Table 8.

Innovative and emerging drugs for chronic pruritus

Botulinum Toxin

The ability of botulinum neurotoxins (BoNTs) to attenuate transmitter release from afferent terminals provides a rationale for studying its effect on pruritus. A 2018 study demonstrates the long-lasting anti-pruritic effects of two BoNT serotypes (BoNT/A1 and BoNT/B1), in a murine pruritus model, using two different mechanistically driven pruritogens and indicates that BoNTs may have a direct effect upon mast cell degranulation[66].

Subsequently, Gazerani P. provides some plausible mechanisms underlying the anti-itch (both histaminergic and non-histaminergic) effect of BoNTs, among which the blockade of neurotransmitter release, the blockade of mast cell degranulation, the downregulation of TRPs (Transient Receptor Potential channels), and the inhibition of neuroimmune key players, such as IL-17. Evidence supporting the neuronal, glial, and immunomodulatory effects of botulinum neurotoxins (BoNTs) in reducing itch transmission is presented, and potential future directions are discussed. Further

Table 7. Traditional topical treatments for itching[71].

Drug category	Active substance	Indications
Topical corticosteroids	Hydrocortisone 1% Betamethasone valerate 0.1 %	Recommended for short-term treatment of chronic pruritus associated with a steroid-responsive dermatosis and secondary inflammatory scratch lesions.
Topical immunomodulators (Calcineurin inhibitors)	Tacrolimus, Pimecrolimus	Recommended as second-line treatment for chronic pruritus associated with atopic dermatitis in patients ≥ 2 years of age and may be considered off label for other inflammatory dermatoses and for secondary inflammatory scratch lesions.
Topical PDE4 inhibitor	Crisaborole	Rapidly relieves atopic dermatitis-associated pruritus and studies suggested its efficacy in patients with psoriasis.
Coolants	Menthol Other phenols	Recommended for topical treatment of chronic pruritus.
Local anesthetics	Lidocaine Pramoxine Polidocanol	Recommended for topical treatment of chronic pruritus.
Capsaicin	Cream 0.025 % to 0.1 % 4 to 6	In case of brachioradial pruritus and notalgia paresthetica, also treatment with capsaicin 8 % patch may be considered.
Cannabinoids	Anandamide Phytocannabinoids Synthetic cannabinoids N-palmitoyl ethanolamine	Recommended for topical treatment of chronic pruritus.

Table 8. Traditional systemic treatments for itching[71].

Drug category	Active substance	Indications
Non-sedative antihistamines	Cetirizine	May be considered for chronic pruritus. In case of insufficient response to the standard dose, up dosing (up to 4 x the standard dose) may be considered.
	Loratadine	
	Fexofenadine	
	Levocetirizine	
	Desloratadine	
	Ebastine	
Systemic glucocorticosteroids	Hydrocortisone	May be considered as short- term treatment of most severe chronic pruritus with great mental distress.
	Prednisone	
	Prednisolone	
	Methylprednisolone	
	Triamcinolone	
	Dexamethasone	
	Betamethasone	
	Deflazacort	
Phototherapy	UVA and UVB light	Anti-inflammatory, immunomodulatory and antiproliferative effects on the skin with pruritic dermatoses.
Cannabinoid	Dronabinol	Efficacious in treating generalized pruritus, especially in systemic diseases such as cholestatic pruritus and uremic pruritus.
Antiepileptic drug	Gabapentin	Particularly indicated in neuropathic pruritus and in chronic prurigo (off label)
	Pregabalin	
Antidepressants:		Efficacious in refractory pruritus; uremic, cholestatic and paraneoplastic pruritus and psychogenic pruritus.
• Tricyclic antidepressants	Doxepine	
	Amitriptyline	
• Selective 5-HT/serotonin uptake inhibitors	Fluoxetine	
	Paroxetine	
	Fluvoxamine	
• Noradrenaline and 5-HT/serotonin antidepressants	Mirtazapine	
Systemic Immunosoppressants	Cyclosporin A	Refractory chronic pruritus associated with inflammatory dermatoses and chronic prurigo.
	Methotrexate	
	Azathioprine	
	Thalidomide	
Biologics	Dupilumab	Approved for the treatment of chronic nodular prurigo.
Opioid receptor agonists and antagonists	Naltrexone	Uremic and cholestatic pruritus.
	Naloxone	
Opioid k-receptor agonists	Difelikefalin	Recommended for adults with moderate to severe nephrogenic pruritus and hemodialysis.
Neurokinin receptor-1 antagonists	Aprepitant	May be considered in recalcitrant cases of chronic pruritus.
	Serlopitant	

Table 9. Innovative and emerging products for allergic skin disorders with chronic pruritus that are currently being studied according to clinicaltrials.gov (active-not recruiting studies) at the time of writing (Sept 23th 2025).

Disorder	Target	Therapeutics
CSU	JAK 1	Povorcitinib
	Bruton Tyrosin Kinase (BTK)	Remibrutinib
CIU	KIT	Barzorvolimab
	c-KIT	Briquilimab
AD, CHRONIC ECZEMA	JAK	Delgocitinib cream
	JAK1/JAK2	Abrocitinib
	Mesenchymal stromal cells	ADSTEM
	Cannabinoid receptors (CB1 and CB2), serotonin receptors (5-HT1A), and transient receptor potential (TRP) channels	Topical Cannabidiol
PN	JAK1/JAK2	Ruxolitinib cream
	IL4-IL13	Dupilumab
	IL4-IL13	Stapokibart Injection
	IL-31	Nemolizumab
	Cannabinoid receptors (CB1 and CB2), serotonin receptors (5-HT1A), and transient receptor potential (TRP) channels	Topical Cannabidiol
ACD	IL4-IL13	Dupilumab
CPUO	None	None

CSU (Chronic Spontaneous Urticaria), CIU (Chronic Inducible Urticaria), AD (Atopic Dermatitis), PN (Prurigo Nodularis), ACD (Allergic contact dermatitis), CPUO (Chronic pruritus of unknown origin)

well-designed clinical trials are needed to establish patient selection criteria, safe and effective dosing, and optimal intervals for repeated administration[67].

Biologics

As more evidence points towards type 2 inflammation as a mechanism for CPUO, with a paradoxical decrease in type 1 inflammation, there has been a heightened interest in therapies that target Th2-associated cytokines such as IL-4, -13, and -31. For example, IL-31 has been found to be significantly increased in the serum of CPUO patients[72]. Therefore, monoclonal antibodies targeting these Th2 cytokines may block them from exerting further downstream effects that lead to CPUO[73]. At the time of writing, several studies are examining new biological drugs or drugs already used for other indications and their outcomes on itching[74].

Janus kinase inhibitors

IL-4, IL-13, and IL-31 and other Th2 cytokines activate the JAK-signal transducer activator of the transcription pathway, which leads to the transcription of proinflammatory cytokines and growth factors that mediate itch. JAK signaling is increased in pruriceptive neurons and JAK inhibitors have been found to have neuromodulatory properties that may attenuate pruritus[61]. JAK inhibitors such as Tofacitinib, Baricitinib, Abrocitinib, and Upadacitinib have potent antipruritic properties and have demonstrated efficacy in several pruritic diseases mainly in atopic dermatitis and psoriasis[75-79]. In particular, Tofacitinib has been investigated for its therapeutic effects in CPUO and found to improve pruritus in CPUO patients[61].

Innovative and emerging drugs for allergic skin disorders with chronic pruritus that are currently being studied (active-not recruiting studies) according

to clinicaltrials.gov at the time of writing, are summarized in Table 9.

The role of dermocosmetics in allergic skin conditions characterized by itch

Moisturizers and emollients function to mitigate the desiccation of the dermis, diminish the rate of Trans epidermal Water Loss (TEWL), enhance comfort, and alleviate pruritus. In skin allergic diseases, the use of moisturizers and emollients can facilitate the reduction in the necessity for the application of topical treatments such as corticosteroids[80]. Additionally, (in AD) they have been shown to reduce the colonization of bacteria[81] and may facilitate the prolongation of the interval between flares and the reduction in the number of flares (secondary prevention)[82]. Successful management strategies ideally should incorporate into the chosen treatment regimen the daily use of easily accessible, efficacious topical preparations designed primarily to tackle the itch. The benefits of these products could conceivably be twofold: physically alleviating the itch stimulus while helping to overcome the psychological need to scratch by allowing for the *ad libitum* application of the product[83]. Cutaneous dysbiosis may amplify barrier dysfunction (in patients with AD) and early-onset barrier dysfunction may facilitate an innate immune response to commensal organisms and, consequently, the development of allergic sensitization[84].

Recent developments have allowed to include pre- and post-biotics in moisturizers providing benefits in balancing the skin microbiome and immune response.

Daily use of emollients is recommended by AD guidelines to restore skin barrier, prevent flares, and further decrease the need of topical steroids to overcome their known side effects[85].

Because of the heterogeneity of causes, phenotypes, patients' age, ethnics, comorbidities, and comedications, no general therapy recommendation for CP can be given[86].

General tips for cleansing

Keeping the skin clean is commonly considered important and a pressing need for patients suffering from skin conditions characterized by itching. Gentle skincare routines, neutral or low pH (5,5), fragrance-free, preservative-free cleanser, and mild non-soap cleansers are preferable. Avoiding harsh soaps, hot water, and excessive scrubbing (scrubs, gels with microgranules and exfoliating products) can help protect the skin's natural barrier. It is advisable to bathe daily (once or twice) and use emollients immediately after bathing. Recommended water temperature range is 27-32 °C, turning off the shower jet while washing to avoid even the slightest trauma caused by the jet. Carefully rinse off the cleansing agents even while taking a shower, avoid using sponges and gloves to massage the skin while washing and rubbing the skin during drying. When using oily products, opt for mineral rather than vegetable oils to avoid or minimize allergenicity, and choose dermatological shampoos, specific for frequent use, making sure to shampoo in the evening to eliminate any allergens and pathogens before going to bed. Cleansing oil, mousse, gel or cream, syndet (synthetic cleanser), dermatological bread, natural Marseille soap, treating soothing physio protective shampoo, make up remover, milk or micellar water cleanser are some examples of cleansing formulations.

Moisturizers and emollients

The ideal emollient should be able to replenish skin lipids and rehydrate the skin, interfere with bilayer lipids, thus regulating inflammation and an immune response with anti-inflammatory action and inhibition of pathogenic skin flora without causing imbalance to commensal organisms.

A short list of ingredients, fragrances and preservatives is required, to avoid late hypersensitization. It should be respectful of the needs of patients and easy to use both by the patient and the caregiver. Single-dose formulations, airless, Intact Formula Exclusive Device (D.E.F.I.) can guarantee its sterility. It is important to prescribe it in adequate quantities, use it freely and frequently, at least 250 g per week in adults, as there are no contraindications for the *ad libitum* application. It is recommended for application to occur immediately after bathing, when the dermis is still slightly hydrated, thus improving water retention in the skin. It should be noted that the degree of dryness of the skin,

the climate and the type of sporting activity, can alter the use of emollients, as well as the texture and the patient's choice regarding creams, ointments or lotions.

The emollients may be enhanced by the incorporation of other ingredients, including ceramides and natural moisturizing factors or plant-derived substances. These products contain putative active ingredients that do not meet the criteria for classification or licensing as topical drugs. However, they have been designated as "emollients plus" by the European guideline since 2018[90,91].

The term "prescription emollient devices" (PED) has recently been introduced in the literature to indicate a class of topical agents developed to "target specific defects in skin barrier function" in individuals with eczema. The PEDs are formulated with a combination of a variety of lipid, ceramide, fatty acid, and natural anti-inflammatory agent mixtures, and

Table 10. Moisturizing and emollient ingredients[80,82,87-89].

Component	Active ingredient	Effect
Humectants	• Urea • Glycerin/Glycerol	Increase attraction and retention of water by the stratum corneum
Occlusives	• Hydrocarbons (petrolatum, mineral oil, paraffin, squalene) • Silicones (dimethicone, cyclomethicone, amodimethicone) • Animal and vegetable fats (lanolin, shea butter, grape seed oil, avocado oil, hemp oil, jojoba oil, sesame seed oil, nut oil) • Fatty acids (lanolin acid, stearic acid) • Fatty and polyhydric alcohols (lanolin alcohol, cetyl alcohol, propylene glycol, butylene glycol) • Wax esters (lanolin, beeswax, stearyl stearate) • Vegetable waxes (carnauba, candelilla) • Phospholipids (lecithin) • Sterols (cholesterol)	Forming a layer on the surface of the skin, reinforce the natural barrier, prevent water loss and reduce the penetration of natural and chemical allergens. Lipids (mineral oil, vegetable oil) act as substitutes for reduced natural skin lipids. Physiological lipids (ceramides, cholesterol) play a signaling role in epidermal differentiation acting on the structural elements of the stratum corneum.
Emollients Protective and fatting substances	• Diisopropyl dilinoleate • Isopropyl isostearate • Castor oil • Propylene glycol • Jojoba oil • Isostearyl isostearate • Octyl stearate	Forming a strong protective film on the skin surface Providing a slightly greasy thin layer with longer- lasting effect on the skin Yielding soft and smooth texture of the skin
Emollient plus	May contain saponins, flavonoids and ribo-flavonoids from protein-free oat seed extracts or bacterial lysates.	Restore and strengthen the skin barrier Reduce inflammation and pruritus in allergic skin diseases Steroid-sparing effect No contraindication to a long-term application
Hydrophilic matrices	Colloidal oatmeal	Forming a physical protective coating over the skin Moisturizing Soothing Anti-inflammatory Protecting the skin barrier Antioxidant
Elements supporting cellular/lipid metabolism	Dexpanthenol	They support metabolism, protein synthesis, and lipid synthesis at the cellular level; they support normal epidermal differentiation and skin repair.

Table 11. A list of anti-itching topical actives.

Active ingredient	Effect
Colloidal oat	Phenolic compound forming a protective film on the skin, acting on its ability to bind and retain water, and acting as a buffer to maintain the correct surface pH. It blocks the release of IL-8,inhibits nuclear factor kappa B, arachidonic acid, and TNF- α, restores skin microbiome balance, thus improving itching, irritation, dryness and severity of eczema[94,95].
Pramoxine hydrochloride	A topical local anesthetic, it blocks voltage-gated sodium channels and prevent nerve signal transmission[96].
Polidocanol	Non-ionic co-surfactant-emulsifier with recognized anti-itching properties in concentrations ranging from 1 to 4%. It is a polyethylene glycol ether of lauryl alcohol inhibiting protease-activated receptor 2 and involved in the histamine-independent itch[97].
Menthol and derivatives	Cyclic terpene alcohol of plant origin evoking a sensation of cold when applied to the skin at low concentrations. It is hypothesized that it acts by activating the cold-sensitive receptor TRPM8 (Transient Receptor Potential Melastatin 8) expressed on the skin's sensory fibers and the opioid k receptors, alleviating pruritus by means of a counterirritant sensation. *Cryosim* is a synthetic TRPM8 agonist with cooling and anti-itch effects, at the moment under investigation[98-100].
Capsaicin (cream 0.05% 4 times or a recently developed 8% capsaicin patch single daily application)	Natural alkaloid derived from chili peppers, capable of desensitizing the TRPV1 receptor (crucial role in pain and itch transmission). It desensitizes and locally ablates the sensory endings that express TRPV1, thus limiting the transmission over time via these nerve fibers. It accelerates skin barrier recovery and alleviates AD-like symptoms. It inhibits the release of pruritogenic neuropeptides substance P and CGRP. *Asivatrep* is a topical TRPV1 antagonist that relieves itch and inflammation, currently in clinical trials for atopic dermatitis[101-104].
Lycocalcone A	Flavonoid extracted from the root of *Glycyrrhiza inflata* (Chinese licorice) inhibiting NF-κB–mediated cytokine release, T cell proliferation, and attenuating cutaneous neuroinflammation[105,106].
N-palmitoylethanolamine	Endocannabinoid-targeting component that can decrease the sensation of itch by increasing the lipid content in the barrier. It Inhibits TRPV1 ion channel[96,107-110]. Inizio moduloFine modulo
Postbiotics (*Aquaphilus dolomiae* extract)	They inhibit the activation of protease-activated receptor 2 and reduce the secretion of cytokines by T helper cells (Th1, Th2, and Th17)[111-113].
Non-replicative probiotic fractions (Vitreoscilla filiformis extract)	It binds to TLR2 (surface of all skin cells), it exerts stimulation on the cells via the TLRs, and mimics action shared with beneficial skin microorganisms[114,115].
Niacinamide	Vitamin B3 amide may reduce pruritus by stimulating ceramide synthesis and inhibits NF-κB signaling, thereby reducing pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and alleviating xerosis-related pruritus[116].
Zanthalene and Biomimetic peptides with neurosensory action	Zanthalene is a CO_2 extract obtained from the fruit of Sichuan pepper, a Chinese spice known for its chemestetic properties with a strong anti-itching action. Its alkylamides reduce skin sensitivity. In vitro tests showed a transitory synaptic transmission block which seems to be responsible for the marked anti-itching and anesthetic-like actions observed[117]. Neuromodulatory agents act on neuromuscular synaptic transmission and on receptors activated by thermal stimuli. If lipophilic in nature, they are also suitable for a wide range of formulations[118].

Active ingredient	Effect
Bisabolol	α-bisabolol is a natural monocyclic sesquiterpene present in the essential oil with strong, dose dependent, binding affinity to the active site of the pro-inflammatory proteins[119].
Vegetable oils Olea europaea (olive oil), Helianthus annus (sunflower seed oil), Cocos nucifera (coconut oil), Simmondsia chinesis (jojoba oil), Avena sativa (oat oil), and Argania spinosa (argan oil).	Compounds with antimicrobial, antioxidant, anti-inflammatory, and anti-itch properties, making them attractive alternative and complementary treatments for xerotic and inflammatory dermatoses associated with skin-barrier disruption[120].
Vit E (Tocopherols and tocotrienols)	They have lipophilic properties which allow them to travel down to the deeper stratum corneum layer within the cell membranes through sebaceous gland secretions and protect them from oxidative damage. Study about management of AD in young children demonstrated a reduction of pruritus intensity measured through SCORAD index through the improvement in terms of TEWL and erythema by tocotrienol enriched moisturizers[121].
Beta Glycyrrhetinic Acid	It inhibits 11β-hydroxysteroid dehydrogenase, prolonging the action of endogenous cortisol in the skin (local cortisone-like effect), and reduces the release of pro-inflammatory cytokines (IL-1β, TNF-α)[122,123].

Abbreviations: TRPM8: Transient receptor potential cation channel subfamily member 8, TRPV1: Transient receptor potential vanilloid 1, CGRP: Calcitonin gene-related peptide.

ratios, including glycyrrhetinic acid, as well as additional ingredients designed to alleviate itching and inflammation[82,92].

A list of moisturizing and emollient ingredients is presented in Table 10 [80, 82,87-89].

Anti-itching actives

As skin barrier damage can cause pruritus, topical therapies that target keratinocytes, nerves and itch receptors near the stratum corneum may provide significant relief for itch[93].

Apart from tailoring the underlying cause/disease, itch severity, body site, lifestyle, climate and age, improved knowledge of the structure of the skin and underlying mechanisms of keratinocyte differentiation have enabled a more rational dermo cosmetic approach aiming to reduce pruritus with a good adherence rate which strongly influence an achievable routine and a favorable disease outcome. To address the uncontrollable urge to scratch, it may be helpful to recommend soothing, anti-itch emollient sprays that quickly relieve the itching sensation, require a light massage of the skin, and distract from the desire to scratch.

A list of supplementary ingredients with anti-itch properties is summarized in Table 11.

Sun protection

Sun protection must be part of a proper daily skincare routine, especially if the skin is damaged by barrier imbalances or actual pathologies. Ideal sun protection should contain specific sunscreen (micronized mineral filters) with SPF 50+ and specific for the skin disease, effectively protect against long and short UVA/UVB rays and be able to prevent post-inflammatory hyperpigmentation.

It should have creamy, non-greasy texture, easy application without any white marks.

Water-resistant, fragrance-free sunscreens that contain no chemical filters, alcohol, or parabens, and that are metal-tested and formulated for sensitive skin, are recommended for allergic skin diseases characterized by pruritus.

Formulations with photostable UVA and UVB filters and antioxidant actives to defend against free radicals generated by IR and UV rays are preferable. Aiming to promote the natural repair mechanisms of the barrier function, it should be enriched with Nicotinamide and ß-Glucan or Vit E.

Conclusion

Evolutionarily conserved to expel ectoparasites and aid in the clearance of toxins and noxious environmental stimuli, pruritus can be a behavioral extension of type 2 immunity by evoking scratching and, in the case of a disease, can become chronic as well as highly pathologic.

Recent advances in itch biology have provided critical new insight into a variety of novel therapeutic avenues for chronic itch in the setting of several allergic disorders.

In chronic pruritus, the correct diagnosis and treatment of the underlying disease are mandatory, as well as patient education and information on the cause and course of symptoms. All aspects of the disease must be addressed, not solely the objective of itch relief itself. Meticulous avoidance of allergenic and irritating agents is advisable, as well as gloves (cotton + rubber), protective clothing, and sleep hygiene. In some cases, an individual assessment and treatment of psychiatric or psychosomatic comorbidities and/or body dysmorphism related to scratching injuries are necessary. The daily use of effective and easily accessible topical preparations to address itching needs to be incorporated into the treatment regimen. It is important to avoid scratching with fingernails or sharp objects, temperature changes (e.g. applying ice, cold shower), external triggers such as excessively hot or cold environments, exposure to uncontrolled sun and pollutants, rough fabrics etc., factors that disturb sleep, create anxiety and stressful situations. On the contrary, it is recommended to encourage proper cleansing and drying, moisturizing, emollience, protection of the skin barrier, cosmetic anti-itch strategies (i.e. instantaneous emollient spray), photoprotection.

Dermo cosmetic treatments target the epidermal barrier and interrupt the itch-scratch cycle. It is beneficial in combination with other drugs, it generally has no side effects and is used as an "interval therapy" or to "spare" more powerful drugs.

The interesting prospect is that, as with pharmacological molecules, our understanding of the skin barrier will lead to the development of even more sophisticated formulations capable of acting on specific targets in different disease phenotypes.

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