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Mini-review

Molecular mechanisms and translational biology of uremic pruritus in chronic kidney disease: A critical analysis of recent advances

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Uremic pruritus (UP) is a prevalent and distressing complication in patients with chronic kidney disease (CKD), particularly those undergoing dialysis. Once considered a peripheral symptom of skin dryness or electrolyte imbalance, UP is now recognized as a complex condition involving neuroimmune dysregulation, inflammatory signaling, and altered skin barrier function. Recent experimental studies have identified key molecular mediators such as interleukin-31 (IL-31), tumor necrosis factor-alpha (TNF-α), transient receptor potential channels (TRPV1, TRPA1), and opioid receptor imbalances that contribute to the pathogenesis of pruritus in CKD. Animal models and *in vitro* assays have provided crucial insights into the mechanisms underlying itch generation and neuronal sensitization. This review critically examines recent advances in the molecular biology of UP and explores translational strategies targeting these pathways. Emphasis is placed on experimental findings from the last decade and their relevance in identifying therapeutic targets. Understanding these mechanisms may help guide future development of personalized treatments and improve quality of life for affected patients.

Keywords: CKD-associated pruritus, Renal itch, Pruritogenic cytokines, Neuroimmune modulation, TRP channel signaling, κ-opioid receptor, Skin barrier dysfunction

Introduction

Uremic pruritus (UP), also referred to as chronic kidney disease-associated pruritus (CKDaP), is a persistent and distressing symptom observed in a significant proportion of patients with chronic kidney disease (CKD), particularly in those with end-stage renal disease (ESRD) on maintenance hemodialysis[1]. Epidemiological studies report that UP affects approximately 40–60% of patients undergoing dialysis worldwide**,** with varying prevalence across regions and dialysis modalities[2, 3]. The condition not only impairs sleep and quality of life but is also associated with increased morbidity and mortality in CKD patients[4]. Although previously attributed to skin dryness or accumulation of uremic toxins[2,3], current evidence recognizes UP as a multifactorial disorder involving neuroimmune dysregulation[5]**,** inflammatory cytokine signaling[6-8]**,** opioid receptor imbalance[9,10] andcutaneous barrier dysfunction[3]**.** Recent advances in experimental biology have uncovered critical insights into the molecular mechanisms underlying UP, including the identification of pruritogenic cytokines such as interleukin-31 (IL-31)[11], the role of sensory neurons and transient receptor potential (TRP) channels[12], and the involvement of keratinocyte-derived mediators[3,13].

These discoveries have facilitated the emergence of novel therapeutic targets, including κ-opioid receptor (KOR) agonists[9,14]TRPV1 inhibitors[12,15] and biologic agents directed against neuroimmune pathways[16]. The aim of this review is to synthesize recent experimental and molecular evidence related to the pathogenesis of UP, critically analyze emerging translational findings, and identify potential targets for future therapeutic interventions.

Material and Methods

This review is based on a structured literature search of peer-reviewed publications related to the molecular biology and pathogenesis of uremic pruritus (UP) in chronic kidney disease (CKD). The primary databases searched were PubMed, Web of Science, and Scopus**,** covering literature published from January 2010 to March 2024. The search was conducted using combinations of the following keywords: *"uremic pruritus"*, *"CKD-associated pruritus"*, *"renal itch"*, *"interleukin-31"*, *"opioid*

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receptor imbalance", *"TRPV1/TRPA1 in pruritus"*, and *"neuroimmune signaling in kidney disease"*.

A total of 312 records were initially identified. After removal of duplicates, 276 studies were screened by title and abstract of these, 158 articles met inclusion criteria, comprising original experimental studies (*In vivo* animal models, *in vitro* cellular assays, and molecular pathway analyses) and selected clinical studies that provided mechanistic insights. 118 articles were excluded due to irrelevance, lack of mechanistic focus, or insufficient experimental detail. Review articles, clinical guidelines, and case series were included only when they offered relevant mechanistic insights or supported experimental observations. No unpublished data or personal communications were used in this review.

Molecular and cellular mechanisms of uremic pruritus

Proinflammatory cytokines and immune modulation

Uremic pruritus (UP) in chronic kidney disease (CKD) is increasingly recognized as a result of significant immune dysregulation[14]. Recent experimental studies have shown that the levels of proinflammatory cytokines such as interleukin-31 (IL-31)[11], interleukin-6 (IL-6)[17], and tumor necrosis factor-alpha (TNF-α)[14] are elevated in patients with advanced CKD. IL-31, in particular, plays a crucial role as it is produced by activated Th2 lymphocytes[18] and interacts with its receptor complex (IL-31RA/oncostatin M receptor) expressed on sensory neurons and keratinocytes[11]. Animal models demonstrate that administration of IL-31 induces scratching behaviour and neuronal activation[10,11], highlighting its pivotal role in initiating and propagating the itch response via a neuroimmune feedback loop.

Opioid receptor dysregulation

Another key mechanism involves dysregulation of the endogenous opioid system[8,9]. In uremia, μ-opioid receptors (MORs) are upregulated while κ-opioid receptors (KORs) are downregulated[8,15], particularly within the dorsal root ganglia (DRG) and skin[15]. This imbalance is critical, as MOR activation enhances itch signaling[8,19], whereas KOR activation normally inhibits neuronal excitability[8,9]. Preclinical studies have shown that KOR agonists, such as nalfurafine, significantly reduce scratching behaviours in CKD animal models[6,13,20], supporting the therapeutic potential of targeting this pathway.

Transient receptor potential channels and neural sensitization

Transient receptor potential (TRP) channels, especially TRPV1 and TRPA1, play a critical role in itch sensory transduction in UP[9,11,21]. These molecular sensors, when activated by pruritogens such as IL-31[11], cause calcium influx, neuronal depolarization, and itch perception. Elevated TRPV1 expression has been observed in the skin of CKD patients and in animal models[9,11] TRPV1 antagonists significantly attenuate itch-related behaviours in experimental studies[11,14,21] making them promising therapeutic targets.

Skin barrier dysfunction and keratinocyte signaling

Skin barrier dysfunction is another contributor to UP[3,22]. Patients with CKD frequently experience xerosis (dry skin), linked to reduced synthesis of epidermal lipids and downregulation of structural proteins such as filaggrin and loricrin[3,22]. *In vitro* studies have shown that uremic plasma disrupts keratinocyte function, increasing transepidermal water loss and the release of inflammatory cytokines and growth factors[22,23]. This barrier breakdown facilitates irritant penetration, amplifies local inflammation, and activates sensory nerve endings, perpetuating the itch cycle[22].

Central sensitization

Beyond peripheral mechanisms, central sensitization contributes to the chronicity of UP[24,25]. Animal studies indicate that glial activation in the spinal dorsal horn enhances neuronal excitability and reduces endogenous inhibitory control[24]. Immunohistochemical analyses show elevated expression of astrocytic marker GFAP (glial fibrillary acidic protein), activation of microglial p38 MAPK signaling, and increased levels of substance P and neurokinin-1 receptor (NK-1R)[24,25]. These findings suggest that central nervous system pathways actively amplify CKD-associated itch. This interplay between peripheral and central mechanisms is summarized in Fig. 1.

Recent advances in experimental biology have significantly expanded our understanding of the molecular and neuroimmune mechanisms underlying uremic pruritus (UP)[4,14,9]. A variety of *in vivo* and *in vitro* models have been developed to replicate the pathophysiological conditions of UP[14,16,26] and to evaluate the effects of targeted therapeutic interventions[6,13,27]. These experimental approaches have provided important insights into the roles of proinflammatory cytokines[11,18], neuronal

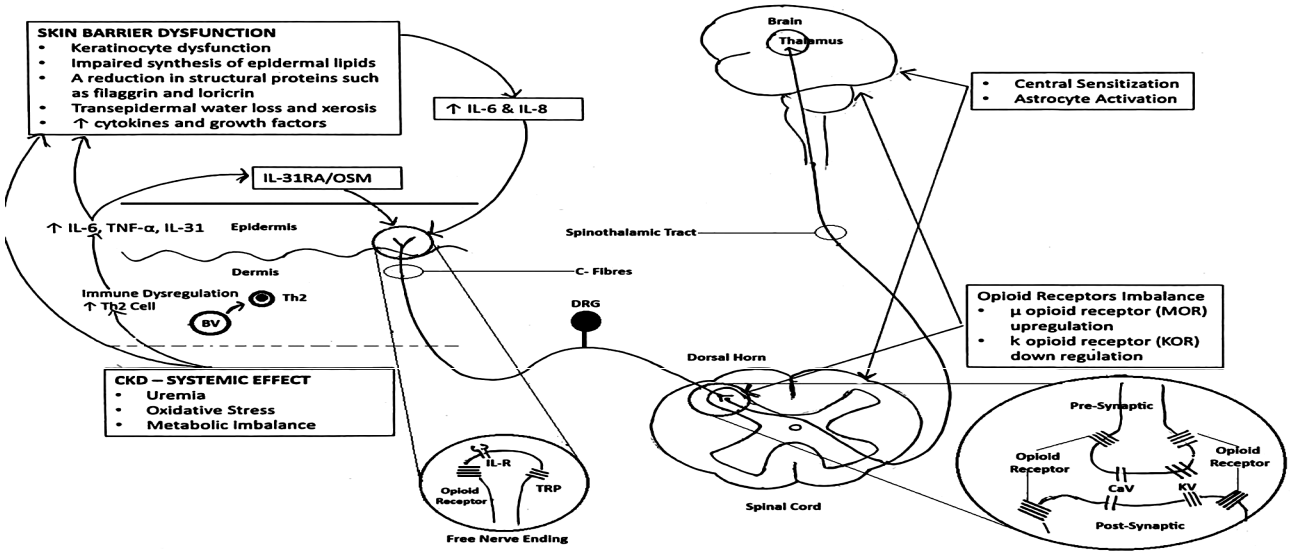

Fig. 1—Schematic representation of molecular and neuroimmune mechanisms in uremic pruritus (UP) associated with chronic kidney disease (CKD). The figure illustrates immune dysregulation (↑IL-31, ↑IL-6, ↑TNF-α), opioid receptor imbalance (↑μ-opioid receptor, ↓ κ-opioid receptor), TRP channel sensitization (↑TRPV1, ↑TRPA1), and skin barrier dysfunction (↓filaggrin, ↓loricrin, ↑NGF, ↑TEWL). Central sensitization is also shown, involving astrocytic activation (↑GFAP), microglial p38 MAPK, and upregulation of substance P and NK-1R, which collectively amplify chronic itch.

sensitization[11,21], epidermal barrier disruption[22,23], and central nervous system alterations[24,25] in CKD-associated itch.

***In vivo* models of uremic pruritus**

Rodent models, particularly murine models of chronic kidney disease, have been instrumental in elucidating the mechanisms of UP[14,16,26]. CKD in these models is typically induced through 5/6 nephrectomy, adenine-enriched diets, or administration of uremic toxins[14,16]. These animals exhibit spontaneous scratching behaviour, which is quantifiable and closely associated with elevated serum levels of IL-31, histamine-independent mediators, and altered expression of opioid and TRP receptors in both skin and dorsal root ganglia[8,9,11]. Importantly, these models have also been useful in evaluating the therapeutic efficacy of pharmacological agents. For instance, systemic administration of κ-opioid receptor (KOR) agonists such as nalfurafine significantly reduces scratching frequency[6,13,20], while antagonists of TRPV1 channels attenuate neuronal hyperexcitability and itch signaling[11,14]. Thus, animal models provide a robust translational platform to investigate both the pathophysiology and potential therapeutic targets of UP.

***In vitro* keratinocyte and sensory neuron models**

Complementary insights have been gained from *in vitro* studies using primary human keratinocytes and immortalized cell lines such as HaCaT. Exposure of these cells to uremic serum results in downregulation of structural barrier proteins including filaggrin and loricrin[22], along with increased secretion of inflammatory mediators such as IL-6, IL-8, and nerve growth factor (NGF)[17,23]. These changes impair skin barrier integrity and contribute to peripheral sensitization. Similarly, neuronal models such as dorsal root ganglion (DRG) cultures have been used to examine the effects of uremic mediators. IL-31 stimulation in these systems induces calcium influx, upregulation of TRPV1 channels, and increased release of neuropeptides, closely mirroring the findings observed in vivo[11,18,21]. Together, these models highlight the reciprocal role of keratinocytes and sensory neurons in amplifying uremic itch.

Molecular profiling and genomic studies

Molecular profiling approaches have further advanced mechanistic understanding of UP. Gene expression analyses, including RNA sequencing (RNA-seq) of pruritic versus non-pruritic CKD skin samples, have revealed differential regulation of genes involved in neuro immune communication, ion channel function, and inflammatory signaling pathways[28,29,30]. Notably, overexpression of IL31RA, TRPA1, and NPY1R has been associated with enhanced pruritoceptive signaling[29]. In addition, proteomic studies of serum and skin from CKD

patients with UP have identified alterations in proteins related to lipid metabolism, immune response, and neuronal growth[30,31]. These molecular findings not only provide novel mechanistic insights but also suggest potential biomarkers for disease severity and treatment response.

Translational significance of experimental findings

The insights obtained from experimental models have guided the development of several promising therapeutic approaches. Nalfurafine, a centrally acting selective KOR agonist, has demonstrated efficacy in reducing pruritus in animal models and clinical trials[6,13,20], leading to its approval in Japan for the treatment of UP in hemodialysis patients. Similarly, difelikefalin, a peripherally restricted selective KOR agonist, has been approved by the U.S. FDA for CKD-associated pruritus, acting primarily on peripheral nerve endings. Gabapentinoids such as gabapentin and pregabalin, which modulate neuronal calcium channels, have also been shown to attenuate excitatory neurotransmission in DRG neurons and provide symptomatic relief in UP[29,32-34]. Beyond these agents, biologic therapies targeting IL-31, IL-4/IL-13, and neurokinin-1 receptor (NK-1R) are currently under active clinical investigation[27,35]. Moreover, TRPV1 antagonists, cannabinoid receptor modulators, and topical barrier-enhancing formulations are being explored as adjunctive or standalone therapies[9,11,14,26,36]. Taken together, these findings underscore the translational value of experimental research and highlight the potential for personalized therapeutic approaches based on specific molecular pathways implicated in CKD-associated pruritus. A summary of the key molecular pathways, associated experimental findings, and their therapeutic relevance is provided in Table 1.

Discussion

Recent experimental research has substantially advanced our understanding of uremic pruritus (UP) as a multifactorial disorder driven by immune, neuronal, epidermal, and central mechanisms[4,11,14]. Among these, interleukin-31 (IL-31) has emerged as one of the most consistently identified pruritogenic cytokines, supported by both clinical observations and mechanistic studies in CKD animal models[10,11,18]. The expression of IL-31 receptors on dorsal root ganglia (DRG) neurons and keratinocytes provides a unifying explanation for peripheral sensitization in UP[11,18]. Nevertheless, IL-31 levels are not uniformly elevated across all patient cohorts[18], suggesting significant heterogeneity in pathogenic pathways and underscoring the likelihood that UP arises from multiple overlapping mechanisms rather than a single dominant mediator.

Dysregulation of the endogenous opioid system represents another central contributor to CKD-associated itch. An imbalance between μ-opioid receptor (MOR) activation, which promotes pruritic signaling, and κ-opioid receptor (KOR) downregulation, which normally exerts inhibitory

Table 1 — Molecular mechanisms contributing to uremic pruritus in chronic kidney disease and their relevance to experimental and translational research

Pathophysiological Mechanism	Key Molecules/Targets	Experimental Findings	Therapeutic Implications
Immune Dysregulation	IL-31 ↑, IL-6 ↑, TNF-α ↑	IL-31 elevated in CKD and induces scratching in animal models; IL-6 and TNF-α associated with systemic inflammation and disease severity	IL-31 antagonists, anti-cytokine therapies
Opioid Receptor Imbalance	μ-opioid ↑, κ-opioid ↓	μ-opioid receptor activation promotes itch; reduced KOR expression in skin/DRG; KOR agonists (nalfurafine, difelikefalin) reduce scratching in CKD models	Nalfurafine, Difelikefalin
TRP Channel Sensitization	TRPV1 ↑, TRPA1 ↑	Upregulated in CKD skin and DRG; mediate Ca^{2+} influx, neuronal depolarization, and itch signaling	TRPV1/TRPA1 antagonists
Skin Barrier Dysfunction	Filaggrin ↓, Loricrin ↓, NGF ↑	Uremic plasma disrupts keratinocyte function; increases transepidermal water loss (TEWL) and cytokine release	Barrier-enhancing topicals, NGF inhibitors
Central Nervous System Changes	Astrocytic marker GFAP ↑, Microglial p38 MAPK ↑, Substance P ↑, NK-1R ↑	Glial activation in spinal dorsal horn enhances neuronal excitability and amplifies itch	Central neuromodulators, gabapentinoids

[CKD, chronic kidney disease; DRG, dorsal root ganglion; GFAP, glial fibrillary acidic protein; KOR, κ-opioid receptor; MOR, μ-opioid receptor; NGF, nerve growth factor; NK-1R, neurokinin-1 receptor; TEWL, transepidermal water loss; TRP, transient receptor potential; TRPV1, transient receptor potential vanilloid 1; TRPA1, transient receptor potential ankyrin]

effects, has been well documented[8,9,15]. Although KOR agonists such as nalfurafine have shown promising clinical efficacy[6,13,20], their precise mechanisms of action remain incompletely understood, and the potential for long-term neural adaptations requires further evaluation[20]. Transient receptor potential (TRP) channels, particularly TRPV1 and TRPA1, also represent compelling therapeutic targets owing to their dual involvement in pain and itch signaling[9,11,21]. Preclinical studies demonstrate that inhibition of these channels effectively reduces pruritic behavior[11,14,21]. However, concerns regarding off-target systemic effects limit their broader clinical application, emphasizing the need for localized delivery systems or receptor-specific modulation strategies.

Skin barrier dysfunction has been another consistent finding in both *in vitro* and clinical studies, with downregulation of proteins such as filaggrin and loricrin contributing to xerosis and local inflammation[22,23]. While these experimental data are compelling, translation into clinically quantifiable outcomes remains limited. Moreover, existing experimental models often fail to capture the chronic, fluctuating, and heterogeneous clinical presentation of UP[35]. This gap highlights the limitations of current preclinical systems and the urgent need for more representative models that integrate the complex interplay of systemic inflammation, neuronal sensitization, and epidermal barrier dysfunction.

In summary, while key molecular pathways and therapeutic targets have been identified including IL-31, opioid receptor imbalance, TRP channel sensitization, and epidermal dysfunction the interplay between these mechanisms, variability among patient populations, and limitations of experimental models continue to constrain progress. Moving forward, a more integrated, multi-pathway research approach, combining molecular, neuronal, and skin biology with advanced preclinical systems, will be essential to bridge the gap between mechanistic insights and effective treatment strategies.

Future directions

Future research on uremic pruritus (UP) should prioritize clarifying the heterogeneity of its underlying mechanisms across different patient populations[18,35]. Given that IL-31 and other mediators are not consistently elevated in all cases, it is likely that multiple pathogenic pathways coexist, varying by genetic, environmental, and treatment-related factors. To address this complexity, there is a pressing need for more representative experimental models that better capture the chronicity, systemic inflammation, neuronal sensitization, and skin barrier dysfunction characteristic of CKD-associated pruritus[35,37].

Emerging technologies hold particular promise in this regard. Multi-omics approaches, including genomics, transcriptomics, proteomics, and metabolomics, can provide comprehensive molecular signatures of UP and identify novel biomarkers predictive of disease severity or therapeutic response[29,30]. Similarly, patient-derived organoid modelsandskin–nerve co-culture systems may more accurately replicate the neuroimmune and barrier interactions that drive chronic itch, thereby serving as powerful translational tools for drug discovery.

In addition to mechanistic research, future therapeutic strategies should emphasize multi-targeted interventionsthat act on both peripheral and central components of the itch pathway[24,25,31]. Integration of molecular profiling with clinical response data could facilitate the development of personalized medicine approaches, ensuring that treatment is tailored to the specific molecular drivers in each patient. Finally, the identification of robust biomarkers and the incorporation of advanced translational platforms will be critical for guiding therapy, monitoring treatment response, and accelerating the clinical adoption of mechanism-based interventions.

Conclusion

Uremic pruritus (UP) in chronic kidney disease (CKD) is a multifactorial disorder involving immune dysregulation, neuronal sensitization, opioid receptor imbalance, epidermal dysfunction, and central mechanisms. Key molecular drivers such as IL-31**,** TRPV1/TRPA1 channels**,** andκ-opioid receptors have been identified. Advances in experimental models and molecular profiling have enabled the development of emerging therapies, including KOR agonists, TRP antagonists, and biologics. Future integration of multi-omics, organoid models, and biomarker-drivenapproaches offers the potential forpersonalized treatmentsthat can improve outcomes and quality of life in CKD patients with pruritus.

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Conflictofinterest

The authors have no conflict of interest to declare.

References

1 Kremer AE, Martens JJ, Kulik W, Rueff F, Kuiper EM, Van Buuren HR, Van Erpecum KJ, Schaap FG, Reijngoud DJ, Elferink RP & Beuers U. Lysophosphatidic acid is a potential mediator of cholestatic pruritus. *Gastroenterology*, 139 (2010) 1008.

2 Liu Y, Dai X, Yu H, Zhou Y, Wei H, Huang Y, Gao X, Zhang C & Liang L. IL-31 expression induces pruritus and Th2 cytokine expression in atopic dermatitis-like skin inflammation. *J Invest Dermatol*, 136 (2016) 1064.

3 Mettang T & Kremer AE. Uremic pruritus. *Kidney Int*, 87 (2015) 685.

4 Shirazian S, Aina O, Park Y, Chowdhury N, Leger K, Hou L, Miyawaki N & Fishbane S. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. *Int J Nephrol Renovasc Dis*, 10 (2017) 11.

5 Wikström B. Itchy skin a clinical problem for haemodialysis patients. *Nephrol Dial Transplant*, 22 (2007) v3.

6 Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H & Suzuki H. Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in hemodialysis patients: a randomized, double-blind, placebo-controlled study. *Nephrol Dial Transplant*, 25 (2010) 1251.

7 Ständer S, Yosipovitch G, Legat FJ, Lacour JP & Lambert J. Targeting the IL-31 pathway for the treatment of pruritus in atopic dermatitis and chronic pruritus. *J Eur Acad Dermatol Venereol*, 30 (2016) 1670.

8 Pontillo C & Mischak H. Urinary peptide-based classifier CKD273: towards clinical application in chronic kidney disease. *Clin Kidney J*, 10 (2017) 192.

9 Kim BS, Inan S, Stander S, Sciascia T, Szepietowski JC, Yosipovitch G. Role of kappa-opioid and mu-opioid receptors in pruritus: Peripheral and central itch circuits. *Exp Dermatol*. 31(2022)1900.

10 Wala-Zielińska K, Świerczyńska-Mróz K, Krajewski PK, Nowicka-Suszko D, Krajewska M, Szepietowski JC. Endogenous Opioid Imbalance as a Potential Factor Involved in the Pathogenesis of Chronic Kidney Disease-Associated Pruritus in Dialysis Patients. J Clin Med. 12 (2023) 2474.

11 Ko MJ, Peng YS, Chen HY, Hsu SP, Pai MF, Yang JY, Wen SY, Jee SH, Wu HY & Chiu HC. Interleukin-31 is associated with uremic pruritus in patients receiving hemodialysis. *J Am Acad Dermatol*, 71 (2014) 1151.

12 Oweis AO, Al-Qarqaz F, Bodoor K, Heis L, Alfaqih MA, Almomani R, Obeidat MA & Alshelleh SA. Elevated interleukin 31 serum levels in hemodialysis patients are associated with uremic pruritus. *Cytokine*, 138 (2021) 155369.

13 Fallahzadeh MK, Roozbeh J, Geramizadeh B & Namazi MR. Interleukin-2 serum levels are elevated in patients with uremic pruritus: a novel finding with practical implications. *Nephrol Dial Transplant*, 26 (2011) 3338.

14 Kimmel M, Alscher DM, Dunst R, Braun N, Machleidt C, Kiefer T, Stülten C, van der Kuip H, Pauli-Magnus C, Raub U, Kuhlmann U & Mettang T. The role of micro-inflammation in the pathogenesis of uraemic pruritus in haemodialysis patients. *Nephrol Dial Transplant*, 21 (2006) 749.

15 Wieczorek A, Krajewski P, Kozioł Gałczyńska M & Szepietowski JC. Opioid receptors expression in the skin of haemodialysis patients suffering from uraemic pruritus. *J Eur Acad Dermatol Venereol*, 34 (2020) 2368.

16 Fishbane S, Jamal A, Munera C, Wen W & Menzaghi F. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med*, 382 (2020) 222.

17 Leong SO, Tan CC, Lye WC, Lee EJ & Chan HL. Dermal mast cell density and pruritus in end-stage renal failure. *Ann Acad Med Singap*, 23 (1994) 327.

18 Assounga AG, Bascoul S, Canaud B, Bouya PA, Vendrell JP, Sciolla JP, Mourad G, Baldet P, Serre A & Mion C. A study of beta 2-microglobulin skin deposits in dialyzed patients and healthy controls. *Am J Kidney Dis*, 15 (1990) 556.

19 Phan NQ, Bernhard JD, Luger TA & Ständer S. Antipruritic treatment with systemic μ-opioid receptor antagonists: a review. *J Am Acad Dermatol*, 63 (2010) 680.

20 Szepietowski JC, Thepen T, Van Vloten WA, Szepietowski T & Bihari IC. Pruritus and mast cell proliferation in the skin of haemodialysis patients. *Inflamm Res*, 44 (1995) S84.

21 Kremer AE, Feramisco J, Reeh PW, Beuers U & Oude Elferink RP. Receptors, cells and circuits involved in pruritus of systemic disorders. *Biochim Biophys Acta*, 1842 (2014) 869.

22 Yosipovitch G, Duque MI, Patel TS, Ishiuji Y, Guzman-Sanchez DA, Dawn AG, Freedman BI, Chan YH, Crumrine D, Elias PM. Skin barrier structure and function and their relationship to pruritus in end-stage renal disease. Nephrol Dial Transplant. 22 (2007) 3268.

23 Craig AD. Interoception: the sense of the physiological condition of the body, *Curr Opin Neurobiol*, 13 (2003) 500.

24 Keshari S, Sipayung AD, Hsieh CC, Su LJ, Chiang YR, Chang HC, Yang WC, Chuang TH, Chen CL & Huang CM. IL-6/p-BTK/p-ERK signaling mediates calcium phosphate-induced pruritus. *FASEB J*, 33 (2019) 12036.

25 Kabashima K & Irie H. Interleukin-31 as a Clinical Target for Pruritus Treatment. *Front Med (Lausanne*) 12 (2021) 638325.

26 Szepietowski JC, Szepietowski T & Reich A. Efficacy and tolerance of the cream containing structured physiological lipids with endocannabinoids in the treatment of uremic pruritus: a preliminary study. *Acta Dermatovenerol Croat*, 13 (2005) 97.

27 Kinugasa E, Igawa K, Shimada H, Kondo M, Funakoshi S, Imada N, Itami N, Fukazawa N, Takubo R, Kawata Y & Murota H. Anti-pruritic effect of nemolizumab in hemodialysis patients with uremic pruritus: a phase II, randomized, double-blind, placebo-controlled clinical study. *Clin Exp Nephrol*, 25 (2021) 875.

28 Kremer AE, Feramisco J, Reeh PW, Beuers U & Oude Elferink RP. Receptors, cells and circuits involved in pruritus of systemic disorders. *Biochim Biophys Acta*, 1842 (2014) 869.

29 Solak Y, Biyik Z, Atalay H, Gaipov A, Guney F, Turk S, Covic A, Goldsmith D & Kanbay M. Pregabalin versus gabapentin in the treatment of neuropathic pruritus in maintenance haemodialysis patients: a prospective, crossover study. *Nephrology (Carlton)*, 17 (2012) 710.

30 Nofal E, Farag F, Nofal A, Eldesouky F & Alkot R. Gabapentin: A promising therapy for uremic pruritus in hemodialysis patients: A randomized-controlled trial and review of literature. *J Dermatolog Treat*, 27 (2016) 515.

31 Kimata H. Interleukin-31 levels are increased in patients with atopic dermatitis. *Clin Exp Allergy*, 36 (2006) 620.

32 Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E & Celiker H. Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant*, 19 (2004) 3137.

33 Ständer S, Yosipovitch G, Legat FJ, Lacour JP & Lambert J. Targeting the IL-31 pathway for the treatment of pruritus in atopic dermatitis and chronic pruritus. *J Eur Acad Dermatol Venereol*, 30 (2016) 1670.

34 Mathur VS, Lindberg J, Germain M, Block G, Tumlin J, Smith M, Grewal M, McGuire D & ITCH National Registry Investigators. A longitudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol*. 5 (2010) 1410.

35 Simonsen E, Komenda P, Lerner B, Askin N, Bohm C, Shaw J, Hejmanowski C, Donnelly S, Walsh M, Zhang M & Tangri N. Treatment of uremic pruritus: a systematic review. *Am J Kidney Dis*, 70 (2017) 638.

36 Gilchrest BA, Rowe JW, Brown RS, Steinman TI & Arndt KA.Pruritus and xerosis in elderly patients. *Arch Dermatol*, 118 (1982) 153.

37 Shirazian S, Grant CD, Aina O, Park Y, Leger K, Hou L, Mattana J & Charytan DM. Association of pruritus with sleep quality and quality of life in hemodialysis patients. *Kidney Res Clin Pract*, 36 (2017) 277.