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The Systemic Pruritus Paradox: Unraveling the Mysteries of Dry Skin in Systemic Disease

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KEYWORDS
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ABSTRACT:

Introduction: Dry skin (xerosis) and pruritus are among the most common dermatological complaints, yet their significance often extends beyond primary skin disorders. Both symptoms are frequently associated with systemic diseases such as chronic kidney disease (CKD), liver dysfunction, diabetes mellitus, and thyroid disorders. Despite their prevalence and impact on quality of life, no comprehensive synthesis has evaluated xerosis and pruritus as cross-cutting manifestations of systemic disease.

Method: A systematic review was conducted following PRISMA guidelines. Major databases were searched for studies published in the last 10 years that reported xerosis or pruritus in patients with systemic diseases. Eligible studies included observational cohorts, cross-sectional analyses, and clinical trials. Data were extracted on prevalence, pathophysiological mechanisms, and quality-of-life outcomes.

Results and Discussion: Fourteen studies met inclusion criteria, encompassing over 40,000 patients across hepatobiliary, renal, endocrine, and metabolic disorders. Xerosis prevalence ranged from 41% in CKD to over 80% in diabetes mellitus, while pruritus prevalence varied from 28.9% in chronic liver disease to 61.7% in cholestatic cohorts. Mechanistic studies highlighted roles for immune dysregulation (IL-6, IL-31), altered lipid composition, impaired sweat/sebaceous gland activity, and neurocutaneous sensitization. Across conditions, xerosis and pruritus were consistently associated with sleep disturbance, anxiety, depression, and reduced quality of life. Several studies also linked moderate-to-severe pruritus with higher hospitalization and mortality risk in CKD.

Conclusion: Xerosis and pruritus are highly prevalent, clinically significant manifestations of systemic disease. Their recognition as more than secondary complaints underscores their potential as low-cost diagnostic markers and targets for multidisciplinary management. Standardized assessment tools and interventional trials are urgently needed to determine whether effective treatment of these symptoms can improve both dermatological and systemic outcomes.

1. Introduction

Dry skin (xerosis) and pruritus are among the most common dermatological complaints encountered in clinical practice, yet their significance often extends beyond primary skin disorders [1]. Xerosis, characterized by reduced stratum corneum hydration and

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impaired barrier function, is frequently associated with systemic conditions such as chronic kidney disease (CKD), liver dysfunction, diabetes mellitus, hematologic malignancies, and endocrine disorders. Pruritus, defined as an unpleasant sensation provoking the desire to scratch, similarly represents a multifactorial symptom that may serve as a cutaneous marker of systemic disease [2].

The burden of xerosis and pruritus is substantial, not only due to their prevalence but also because of their impact on quality of life [3]. Patients with systemic diseases often report sleep disturbance, psychological distress, and impaired daily functioning as a result of persistent itch and skin discomfort [4]. These symptoms may precede or parallel systemic disease progression, highlighting their potential role as early diagnostic indicators [5].

Recent advances in dermatology and internal medicine have emphasized the neuroimmune and barrier-related mechanisms underlying xerosis and pruritus. Dysregulation of cytokine pathways, alterations in peripheral nerve sensitization, and systemic metabolic changes have all been implicated in the pathogenesis of these symptoms across diverse systemic conditions [6]. Importantly, recognition of xerosis and pruritus as more than secondary complaints underscores the need for a comprehensive synthesis of evidence linking skin symptoms to systemic disease [7].

Despite the growing body of literature, no systematic review has comprehensively evaluated xerosis and pruritus as cross-cutting manifestations of systemic disorders. This review aims to fill that gap by synthesizing current evidence on their prevalence, pathophysiological mechanisms, and clinical implications across systemic diseases. By unmasking systemic disease through skin symptoms, this work seeks to inform both dermatological and multidisciplinary care, while identifying opportunities for earlier diagnosis and improved patient outcomes.

2. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The protocol was prospectively registered in PROSPERO CRD. We systematically searched PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library for studies published between January 2015 and October 2025, using a combination of controlled vocabulary and free-text terms including “xerosis,” “dry skin,” “xeroderma,” “pruritus,” “itch,” and “systemic disease.”

Eligible studies included observational studies and randomized controlled trials reporting xerosis or pruritus in patients with systemic diseases such as chronic kidney disease, liver disease, diabetes mellitus, hematologic malignancies, and endocrine disorders. Case reports, conference abstracts without full text, animal studies, systematic review and meta analysis, and non-English publications were excluded. Two reviewers independently screened titles, abstracts, and full texts, with disagreements resolved by consensus or a third reviewer. Data were extracted using a standardized form capturing study characteristics, assessment methods, prevalence, severity, and quality-of-life outcomes. Risk of bias was assessed using the Newcastle–Ottawa Scale for observational studies and the Cochrane Risk of Bias 2.0 tool for randomized trials. Due to anticipated heterogeneity, findings were synthesized narratively.

3. Results

Study Selection

The initial search identified 15,176 records across PubMed, Cochrane Central, MDPI, and Taylor & Francis. After removal of duplicates (n = 7,482) and records not meeting study design criteria (n = 10,743), 4,433 records were screened. Of these, 1,768 were excluded for irrelevance or inability to retrieve full texts. A total of 2,651 full-text articles were assessed for eligibility, with 2,637 excluded due to lack of systemic disease focus, treatment-centered outcomes, or high risk of bias. Ultimately, 14 studies were included for qualitative synthesis.

Study Characteristics

The included studies were conducted across diverse regions, including Asia (Japan, Indonesia, Turkey), Europe (Italy, Netherlands, Poland), North and South America (USA, Colombia), and multinational cohorts. Study designs comprised cross-sectional surveys, cohort studies, randomized controlled trials, and retrospective analyses. Sample sizes ranged from small clinical cohorts (n = 4) to large population-based studies (n > 35,000). The systemic diseases represented were chronic liver disease, diabetes mellitus, thyroid disorders, and chronic kidney disease. The characteristic of included studies can be found in Table 1.

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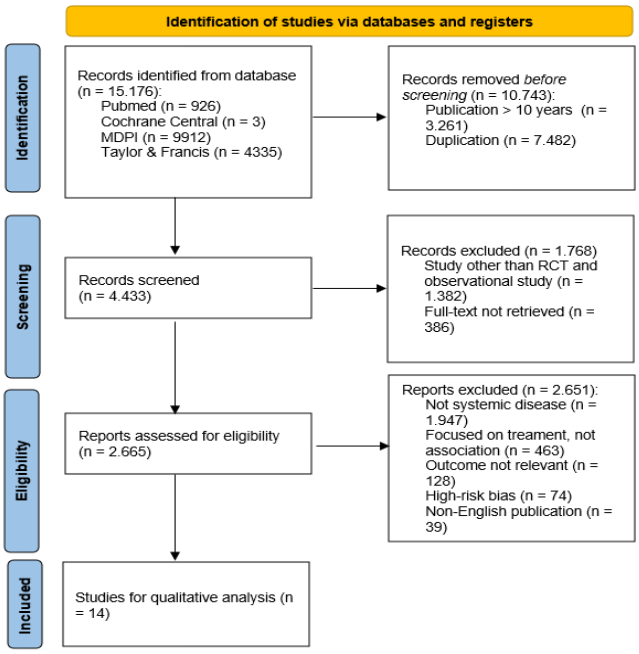

Figure 1. PRISMA Chart

Prevalence of Xerosis and Pruritus

Pruritus and xerosis were consistently reported as common manifestations across systemic diseases. In chronic liver disease, prevalence of pruritus ranged from 28.9% to 61.7%, with some studies reporting universal pruritus in selected cohorts. Among patients with diabetes mellitus, pruritus prevalence reached 85%, with xerosis affecting up to 81.3% of participants. In chronic kidney disease, xerosis and pruritus were reported in 41–70% of patients, with one multinational study documenting xerosis in nearly half of over 35,000 participants.

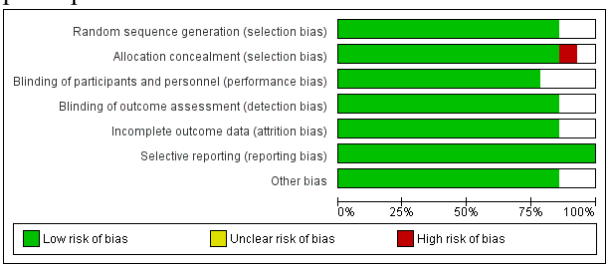

Figure 2. Risk of Bias

Assessment Tools

A wide range of assessment instruments were employed, reflecting heterogeneity in measurement approaches. These included visual analogue scales (VAS), numerical rating scales (NRS), dermatology-specific indices such as the Dermatology Life Quality Index (DLQI) and ODS, as well as systemic disease–specific tools like KDQOL-Q20. Some studies used composite itch scales (e.g., Kawashima's criteria, 10-PSS, Itchy/Quant), while others relied on structured questionnaires.

Impact in Quality of Life

Several studies highlighted the psychosocial burden of skin symptoms in systemic disease. Pruritus and xerosis were significantly associated with anxiety, depressive symptoms, and impaired quality of life. For example, in chronic kidney disease cohorts, up to 80% of patients with pruritus reported depression-related symptoms, while nearly half reported decreased quality of life. Similarly, patients with liver and thyroid disease frequently described moderate to severe pruritus with substantial impact on daily functioning.

4. Discussion

Pruritus and Dry Skin

Pruritus remains a subject of considerable debate due to the challenges in precisely defining and characterizing it. It has often been described indirectly, such as a sensation that triggers the urge to scratch or an uncomfortable irritation of the skin. The neural transmission of itch begins in peripheral nerves and is conveyed to the dorsal horn of the spinal cord. From there, signals cross via the anterior commissure and ascend through the spinothalamic tract to the laminar nuclei of the opposite thalamus. Tertiary neurons within thalamocortical pathways are thought to relay these impulses through the reticular activating system of the thalamus, ultimately reaching multiple regions of the cerebral cortex. Biochemically, pruritus can be induced by mediators such as histamine, prostaglandins, proteases, and substance P [8].

Xerosis cutis refers to a condition of dry skin that arises from multiple contributing factors. It is primarily linked to reduced moisture within the stratum corneum, often caused by diminished activity of sebaceous and sweat glands. Additional mechanisms include impaired filaggrin synthesis, alterations in lipid composition, and intrinsic abnormalities in keratinization. These changes not only lead to dryness but also compromise the integrity of the skin barrier. Clinically, xerosis presents as widespread rough, scaly skin, frequently associated with itching, burning sensations, and increased susceptibility to irritants. Moreover, xerosis cutis can develop as a secondary manifestation of systemic diseases or other comorbid conditions [9].

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Table 1. Characteristic of the Studies

Author, Year	Country	Design	Population	Systemic Disease	Manifestation	Assessment Tools	QoL Impact
Wen, 2025[10]	USA	Cohort	112 patients, mean age of 57 years, consists of 48 male and 64 female	Chronic Kidney Disease	57% patients reported pruritus in WI-NRS, and 42% in KDQOL-Q20	KDQOL-Q20, WI-NRS	80% reported depression-related problems and 67% reported sleep-related problems
Kurniawan, 2022[11]	Indonesia	Cross-sectional	39 patients, ranging from 32-79 years old, consists of 27 male and 12 female	Chronic Kidney Disease	46,1% patients reported pruritus and 100% patients have xerosis	ODS	89% patient with pruritus and 56% patients with xerosis reported decreasing QoL
Rayner, 2017[12]	Multinational	Cohort	35.452 patients in 17 countries	Chronic Kidney Disease	Pruritus reported varies from 26 - 48% in each country	Original questionnaire	54% patients bothered by dry skin and 47% patients have restless sleep
Dwiyana, 2023[13]	Indonesia	Cross-sectional	139 patients, mean age 47.6 years old, consists of 70 male and 69 female	Chronic Kidney Disease	60,4% patients reported xerosis and 40,3% patients reported pruritus	ODS	NA
Dalimunthe, 2024[14]	Indonesia	Cross-sectional	67 patients, mean age 52 years old, consists of 41 male and 26 female	Chronic Kidney Disease	70,1% patients have dry skin	DLQI	26,9% patients reported moderate effect and 7,5% patients reported very large effect on DLQI
Perez, 2024[15]	Colombia	Retrospective observational	4 patients, aged 33-57 years old	Hepatobiliary Disease	Mean of ItchyQuant in patients is 7.5	ItchyQuant	NA
Bollemeijer, 2024[16]	Netherlands	Cross-sectional	5245 patients, ranging from 51-100 years old, consists of 2310 male and 2936 female	Diabetes Mellitus, Renal impariment, liver disease,	Renal impairment is statistically significant to pruritus; meanwhile	NA	Patients with pruritus have reported depressive and anxiety symptoms that

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				thyroid disease	diabetes, liver disease, and thyroid disease are do not have correlation to pruritus		statistically significant
Mazan, 2024[17]	Poland	Cross-sectional	132 patients, aged > 65 years old, consists of 30 male and 102 female	Thyroid disease, Diabetes mellitus, kidney disease	46.67% patients with diabetes mellitus reported pruritus; 23.81% in thyroid disease; and 16.19% in kidney disease	ODS, 10-PSS	NA
Mayo, 2022[18]	USA	Cohort	211 patients consists of 17 male and 194 female	Primary Biliary Cholangitis	81% patients reported pruritus	Patient reported outcome including PBC-40, D-5 Itch, and PROMIS Fatigue	NA
Oeda, 2017[19]	Japan	Cross-sectional	1631 patients, mean age 60 years old, consists of 741 male and 890 female	Chronic Liver Disease	40.3% reported pruritus	VAS	NA
Yoshikawa, 2021[20]	Japan	Cross-sectional	450 patients, ranging from 18-87 years old, consists of 189 male and 261 female	Chronic Liver Disease	53% patients reported pruritus	Kawashima's criteria of pruritus	NA
Karadag, 2022[21]	Turkey	RCT	60 patients, mean age 61 years old, consists of 33 male and 27 female	Cirrhosis Liver	61.7% patients have dry skin and 100% suffering from pruritus	5-D Itch Scale, VAS	There is a significant correlation between dry skin and anxiety
Susanto, 2025[22]	Indonesia	Cross-sectional	97 patients, ranging from 45-60 years old, consists of 37	Diabetes Mellitus	67% patients have dry skin and 100% patients	CM 825 Corneometer, NRS	NA

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			male and 60 female		suffering from pruritus			
Stingeni, 2021[23]	Italy	Cohort	327 patients, aged more than 18 years old	Diabetes Melltisu	81,3% suffering from dry skin	ODS	NA	

KDQOL-Q20: Kidney Disease Quality of Life—Short Form; WI-NRS: Worst Itch Numeric Rating Scale; ODS: Overal Dry Skin Score; NA: not applicable; DLQI: Dermatology Life Quality Indeks; 10-PSS: 10-Item Pruritus Severity Scale; VAS: Visual Analog Scale; RCT: Randomized Controlled Trial; NRS: Numeric Rating Scale

Kidney Disease and Pruritus or Dry Skin

This systematic review identified several studies reporting a high prevalence of xerosis and pruritus among patients with kidney disease, including the chronic kidney disease (CKD), particularly in dialysis populations. In our results, prevalence rates ranged from 41% to over 70%, with one large multinational cohort documenting xerosis in nearly half of more than 35,000 patients. These findings are consistent with recent literature, which estimates that 50–85% of CKD patients experience chronic pruritus, often accompanied by xerosis [24,25].

The pathogenesis of CKD-associated pruritus (CKD-aP) and xerosis is multifactorial, aligning with the heterogeneity observed in our included studies. Reduced sweat and sebaceous gland activity, impaired stratum corneum hydration, and altered lipid composition explain the frequent reports of xerosis. Meanwhile, pruritus is increasingly understood as the result of systemic inflammation, dysregulated opioid receptor signaling, and neuropathic mechanisms. Elevated cytokines such as IL-6 and IL-31, as well as imbalances between μ- and κ-opioid receptor activity, have been implicated in amplifying itch perception [25].

Importantly, our review also highlighted the psychosocial burden of these symptoms. Several included studies reported significant associations between xerosis/pruritus and depression, anxiety, and reduced quality of life, with up to 80% of patients in some cohorts describing mood disturbances. This mirrors recent cohort data showing that moderate-to-severe CKD-aP is linked to higher hospitalization and mortality risks [26]. Thus, the impact of xerosis and pruritus extends beyond dermatological discomfort, influencing both mental health and systemic outcomes.

Hepatobiliary Disease and Pruritus or Dry Skin

Pruritus and xerosis are prominent cutaneous manifestations in hepatobiliary disease, particularly in cholestatic disorders, and our results echo this burden: pruritus prevalence in chronic liver disease ranged from 28.9% to 61.7%, with some cohorts reporting universal itch, alongside notable quality-of-life impairment. These findings align with contemporary evidence that frames cholestatic pruritus as a distinct syndrome driven by bile flow impairment and complex neuroimmune signaling, rather than a mere epiphenomenon of elevated liver enzymes [27].

Mechanistically, cholestatic pruritus is increasingly linked to pruritogens such as lysophosphatidic acid (LPA) and its generating enzyme autotaxin, bile acids, and endogenous opioids. LPA/autotaxin activity appears to sensitize peripheral and central itch pathways, while altered bile acid handling and opioid receptor signaling contribute to neurocutaneous amplification of itch. This model helps explain why symptom severity often diverges from routine biochemical markers and underscores the central role of cholestasis-specific pruritogens in driving clinical distress [27]. Complementary reviews further detail candidate pruritogens and receptor-level mechanisms (including TGR5 and opioid receptors), consolidating the view that cholestatic pruritus emerges from convergent metabolic and neurosensory cues rather than a single mediator [28].

Clinically, our synthesis mirrors the literature's emphasis on substantial psychosocial and functional impact including patients report sleep disturbance, anxiety, and reduced dermatology-specific quality of life (DLQI), consistent with the large effect observed in hepatobiliary cohorts within our results. This burden has catalyzed a stepwise, mechanism-informed treatment approach: bile acid modulation (cholestyramine), pregnane X receptor activation (rifampicin), opioid pathway antagonism (naltrexone), fibrates (e.g., bezafibrate), and more recently ileal bile acid transporter inhibitors and strategies targeting autotaxin/LPA signaling. Such escalation reflects recognition that cholestatic pruritus

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can be refractory and requires alignment of therapy with pathophysiology [27].

Endocrine Disorder and Pruritus or Dry Skin

This systematic review identified that endocrine disorders, particularly diabetes mellitus and thyroid disease, are strongly associated with xerosis and pruritus, with prevalence rates ranging from 67% to 85% in diabetic cohorts and around 47% in thyroid disease populations. These findings are consistent with recent literature, which emphasizes that skin is a frequent target organ of endocrine dysregulation, and cutaneous symptoms may serve as early or prominent indicators of systemic disease [29].

In diabetes mellitus, xerosis is one of the most common dermatological manifestations. The pathogenesis involves autonomic neuropathy leading to reduced sweat gland activity, microvascular damage impairing skin hydration, and hyperglycemia-induced changes in lipid metabolism of the stratum corneum. These mechanisms explain the high prevalence of xerosis and pruritus observed in our included studies, particularly in middle-aged and elderly populations. Chronic itch in diabetes may also be neuropathic in origin, linked to small-fiber dysfunction, which aligns with reports of persistent pruritus even in the absence of visible lesions [30].

In thyroid disorders, xerosis is especially common in hypothyroidism due to reduced eccrine gland secretion and altered epidermal lipid composition, while hyperthyroidism has been associated with pruritus through increased cutaneous blood flow and heightened peripheral nerve sensitivity. Our review found that nearly half of thyroid disease patients reported pruritus, with a significant proportion experiencing moderate to severe symptoms. This supports recent evidence that endocrine-driven skin changes are not only cosmetic but also symptomatic, contributing to discomfort and reduced quality of life [31].

5. Limitations

This study has several limitations that should be acknowledged. First, although the review followed a PRISMA-guided methodology, the included studies were highly heterogeneous in terms of design, population size, and assessment tools for xerosis and pruritus. This variability limited the ability to perform a quantitative synthesis or meta-analysis and may have introduced inconsistency in prevalence estimates. Second, most of the included studies were cross-sectional, which restricts causal inference regarding the relationship between systemic disease and skin manifestations. Third, the reliance on self-reported measures of pruritus and xerosis in many studies may have introduced recall or reporting bias, while objective dermatological assessments were less frequently employed. Fourth, the exclusion of non-English publications may have led to language bias and underrepresentation of data from certain regions. Fifth, publication bias cannot be ruled out, as studies with negative or null findings are less likely to be published. Finally, the relatively small number of high-quality randomized controlled trials and longitudinal studies limits the generalizability of our findings and underscores the need for more robust research to clarify mechanisms and evaluate interventions.

6. Conclusions

The findings of this systematic review carry several important clinical implications. First, the high prevalence of xerosis and pruritus across diverse systemic diseases, ranging from 28.9% in chronic liver disease to over 80% in diabetes and chronic kidney disease cohorts, demonstrates that these symptoms are common, clinically meaningful, and often underappreciated. This underscores the need for clinicians to move beyond viewing dry skin and itch as minor or cosmetic concerns, and instead recognize them as potential early indicators of systemic dysfunction. Future research should prioritize standardized assessment methods, mechanistic studies, and interventional trials to determine whether targeted management of xerosis and pruritus can improve both dermatological and systemic outcomes.

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