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# Targeting kallikrein proteases for dandruff therapy

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**Abstract**

Kallikrein proteases (KPs) are vital enzymes involved in the formation of dermatosomes and are regulated by the body's internal inhibitors. Maintaining a balance between KPs and their inhibitors is essential for promoting a healthy scalp. The scalp specifically contains two KPs: human kallikrein (hK) 5 and hK7, which are encoded by their respective genes. In addition, the serine protease inhibitor Kazal-type 5 (*SPINK5*) gene encodes the lympho-epithelial Kazal-type-related inhibitor (LEKTI), which effectively inhibits both hK5 and hK7. The normal desquamation process relies on the availability and activity of hK5 and hK7, along with their regulation by LEKTI. When LEKTI levels are insufficient, it results in abnormal desquamation characterized by the overactivity of hK5 and hK7. Consequently, KPs, particularly hK5 and hK7, present promising targets for novel treatments aimed at reducing flake formation associated with dandruff. KP inhibitors are crucial components in targeting these proteases. In this review, literature on KPs, dandruff, and their inhibitors was analyzed to elucidate the roles of KPs in dandruff pathogenesis and to evaluate the therapeutic potential of KP inhibitor-based approaches for managing this condition.

**Keywords:** dandruff, protease, LEKTI, kallikrein, *SPINK5*

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## Introduction

Kallikrein proteases (KPs) play a crucial role in the skin and scalp by degrading corneodesmosome proteins, which are vital for the desquamation process. These proteases are tightly regulated by specific inhibitors that limit their enzymatic activity. The genes involved in producing, coordinating, and regulating KPs and their inhibitors are pivotal to the degradation of corneodesmosomes.

Corneodesmosomes are specialized adhesive proteins located in the stratum corneum (SC). They originate as modified desmosomes in the stratum granulosum of the epidermis and are degraded during proper desquamation (1).

The scalp differs from other body regions due to its high vascularization, which supports water retention and thermoregulation (2). Maintaining scalp health is vital to preventing hair and scalp disorders (3). Under dry or oily conditions, KP activity in the scalp increases (4), potentially contributing to dandruff.

This review examines the correlation between KPs and desquamation in the dandruff-affected scalp, the role of KP inhibitors in this process, and the potential of KP inhibitor–based therapies for dandruff. In addition, the influence of sebum production and environmental factors on KP-related desquamation is briefly discussed.

## Methods

A literature review was conducted using PubMed and ScienceDirect, focusing on keywords such as *kallikrein*, *scalp*, *protease*, *inhibitor*, and *dandruff*. Relevant studies were screened and organized in line with the objectives of this review.

## Results

### Correlation of kallikrein proteases with flake formation in the scalp affected by dandruff

Dandruff-related flaking and itch result from a compromised scalp barrier, disrupted corneocyte cohesion, and abnormal desquamation. The biochemical composition of the SC differs significantly between healthy and dandruff-affected scalps, primarily due to imbalanced KP activity and inhibitor levels. This imbalance contributes to corneodesmosome degradation and SC barrier dysfunction (5, 6).

The dominant pathological paradigm identifies *Malassezia* as the primary cause of dandruff. Nevertheless, *Malassezia* presence alone is insufficient, as it is also found on healthy scalps (7). Therefore, it is necessary to reconsider other contributing factors. Dandruff is now recognized as a multifactorial condition influenced by *Malassezia*, sebum overproduction, KPs, water barrier disruption, and environmental factors (Fig. 1).

Human tissue KPs comprise at least 15 (chymo) trypsin-like secreted serine proteases, denoted as human kallikrein (hK)1 through hK15. Among these, hK5, hK6, hK7, hK8, and hK13 are present in the SC, with hK5 and hK7 playing particularly critical roles due to their ability to degrade desmosomes and corneodesmosomes. As a result, hK5 and hK7 are considered key regulators of the desquamation process (8). Their activity is tightly regulated through interactions with specific serine protease inhibitors, including lympho-epithelial Kazal-type-related inhibitor (LEKTI) (9). The enzymatic activity of hK5 and hK7 is pH-dependent; elevated pH levels enhance their activity, leading

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to increased corneodesmosome proteolysis and subsequent barrier breakdown (1).

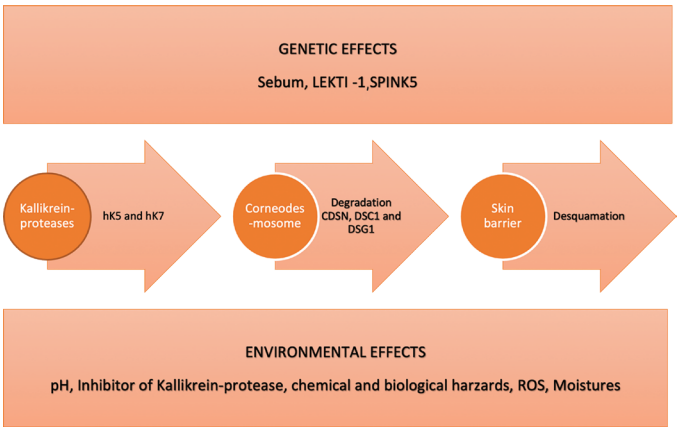


Figure 1 | The impact of kallikrein proteases along with genetic and environmental factors on skin barrier degradation.
LEKTI = lympho-epithelial Kazal-type-related inhibitor, SPINK5 = serine protease inhibitor Kazal-type 5, hK = human kallikrein, CDSN = corneodesmosin, DSC1 = desmocollin -1, DSG1 = desmoglein-1, ROS = reactive oxygen species, SC = stratum corneum.

### Expression of kallikrein proteases in the scalp

All human tissue KPs are encoded on chromosome 19q13.4 and expressed across various tissues, including the scalp, where they regulate desquamation (10). The expression levels of hK5 and hK7 can be either downregulated or upregulated (6).

Regulation of KPs occurs at the transcriptional, translational, and post-translational levels. Overexpression and increased activity of KPs, particularly hK5 and hK7, are implicated in desquamation processes in the scalp. As a result, KPs are considered promising targets for the development of new dandruff therapeutics (10). The activities of hK5 and hK7 contribute to desquamation through the cleavage of desmoglein 1 (DSG1), a process that is potently inhibited by LEKTI (11).

### Regulation of scalp desquamation and its impact on dandruff

SC plays a crucial role in maintaining an effective skin barrier, especially in dandruff-prone scalps, where it relies on intact corneodesmosomes and superficial epidermal tight junctions (TJs). Functional proteins—including corneodesmosomes, desmosomes, TJs, and adherens junctions—are regulated at the genetic or activity level (12). Consequently, SC thickness and scalp surface appearance are influenced by the degradation of corneodesmosomes (13).

Desmosomes are located among keratinocytes in the viable epidermal layers and are vital for intercellular adhesion. During cell differentiation and cornification, desmosomes transition into corneodesmosomes. In the lower SC, corneodesmosomes are positioned around the cell membrane, whereas in the upper SC they are primarily localized at the edges of flattened cells. TJs structures help maintain this unique distribution of corneodesmosomes and protect them from excessive degradation due to overactivity of hK5 and hK7 (14).

Corneodesmosomes form from desmosomes in the uppermost layers of the epidermis and are essential for corneocyte cohesion. The primary extracellular protein components of corneodesmosomes include corneodesmosin (CDSN), desmocollin (DSC) 1, and DSG1. These adhesive proteins are located on the surface of corneodesmosomes and contribute to the formation of junctional structures, such as TJs, which promote corneocyte cohesion (13, 15). The integrity of the SC relies on various biochemical processes that control corneodesmosome degradation. Flaking on the scalp largely results from disruptions in these processes, which compromise corneocyte cohesion and normal desquamation (6). Consequently, the rate at which CDSN, DSG1, and DSC1 degrade at the scalp surface directly impacts the desquamation process (Figs. 2, 3) (15).

The integrity of the SC is preserved in a steady state that allows for controlled desquamation. This balance depends on the regulated rate of corneodesmosome degradation. The primary corneodesmosomal proteins—CDSN, DSG1, and DSC1—are distributed at cell boundaries in the upper SC but are absent from central areas of the SC. In the superficial granular layer, TJs act as barriers, preventing KPs from reaching the central intercellular spaces of the SC while allowing KP access to peripheral corneodesmosomes. This unique structure, resembling a basket-weave pattern, allows selective KP activity in the SC periphery (16). Thus, KPs play an essential role in epidermal physiology, with significant implications for scalp dandruff (Figs. 2, 3) (17).

SC desquamation depends on human tissue hKs, particularly hK5 and hK7 (18). Both are capable of degrading corneodesmosomes, which facilitates desquamation. Serine protease inhibitors can block the activity of hK5 and hK7, thus regulating desquamation (11). hK5 and hK7 have the ability to cleave corneodesmosomal components, including CDSN, DSG1, and DSC1. hK5 can also activate the precursor form of hK7 and degrade all three corneodesmosomal components. In contrast, hK7 cleaves CDSN and DSC1 but not DSG1. Both hK5 and hK7 contribute to desquamation. Maintaining a precise balance between protease activity and protease inhibitors is essential for regulating this process. Uncontrolled activity of hK5 and hK7 can have detrimental effects on the skin barrier function in the scalp (15, 19).

The distribution of corneodesmosomes plays a key role in the cohesiveness and barrier function of the SC in individuals affected by dandruff. In a healthy scalp, corneodesmosomes are confined to the peripheral regions of the corneocytes. However, in dandruff-affected scalps, corneodesmosomes are found both at the periphery and across the entire corneocyte surface. This abnormal persistence of non-peripheral corneodesmosomes contributes to the irregular desquamation observed in dandruff. An imbalance between KP activity and its inhibitor in the SC characterizes the dandruff condition (6).

CDSN is a secreted glycoprotein situated within the core of corneodesmosomes and is covalently bound to the cornified envelope of corneocytes (20). It plays a crucial role in maintaining epidermal barrier function, with its proteolysis acting as a trigger for the desquamation process (21, 22). Proteolytic modifications of CDSN are linked to both the cohesiveness of scalp tissue and the process of scalp desquamation (23).

The two primary adhesion proteins of the corneodesmosome are DSG1 and DSC1. Both can be degraded by hK5 and hK7, facilitating corneocyte sloughing in the SC. The distribution of DSG1 and DSC1 on corneocytes plays a key role in the formation of the SC barrier. DSG1 is predominantly found on the corneocytes of the outermost SC, either at the periphery or covering the entire surface (24).

The KPs hK5 and hK7 have the capacity to activate a G-protein-coupled receptor: protease-activated receptor-2 (PAR2). However, so far there has been no report on the involvement of PAR2 activation in flake formation in dandruff. In atopic dermatitis (AD),

activation of PAR2 has been implicated in skin barrier regulation. Protease-activated PAR2 can drive skin barrier dysfunction (25). Serine proteases, serine protease inhibitors, and PARs are involved in disrupting the epidermal permeability barrier, desquamation, and inflammation, all of which are key factors in various skin disorders (Fig. 4).

The activation or inhibition of PAR2 receptors plays a crucial role in epidermal homeostasis (26). Proteases are essential for maintaining the permeability barrier of the epidermis. Through their direct proteolytic activity, they can specifically activate PARs to signal to cells. Functional PAR-2 is vital for skin barrier homeostasis; however, in conditions like AD, abnormal protease/PAR-2 signaling occurs, marked by irregular serine protease activation and altered PAR-2 expression. This imbalance between proteolytic activity and inhibition is influenced by genetic defects in proteases or their inhibitors, elevated skin surface pH, and the presence of proteolytically active allergens. Overactivity of proteases leads to atypical desquamation, rapid degradation of lipolytic enzymes and antimicrobial peptides, and activation of primary cytokines. Consequently, this disorder can cause inflammation, permeability barrier dysfunction, and damage to the antimicrobial barrier. Therefore, targeting proteolytic enzymes or PAR-2 may provide a therapeutic strategy for dandruff (27). Extracellular endogenous proteases interact with cell-surface receptors, including PARs, with PAR-2 being the most significant of the four known PARs. PAR activation stimulates epithelial cells to open TJs, promoting desquamation (28). The relationship between PAR-2 and dandruff remains an area for further investigation.

Abnormal or delayed desquamation is a non-homeostatic state, characterized by an accumulation of corneocytes on the SC surface, which eventually results in “dry skin” (29). Various skin conditions, including dandruff, are associated with defects in genes encoding the proteolytic components of desmosomes and corneodesmosomes (14). Mutations in genes responsible for encoding desmosomal components are also implicated in several skin disorders (30). The SC barrier function relies not only on its individual components but also on its structural organization (31).

Normal desquamation involves a balanced process of corneocyte production and release from the skin surface, with the proteolytic degradation of corneodesmosomes being a critical final step in desquamation. The SC tryptic enzyme (SCTE), a proteolytic enzyme, plays a key role by degrading these adhesion molecules (32).

Skin integrity is essential for maintaining homeostasis, with the epidermis undergoing continuous self-renewal through a balance between superficial desquamation and keratinocyte proliferation in the basal layer. Epidermal cohesion depends on specialized adhesive junctions—namely, desmosomes and corneodesmosomes—which require precise regulation to function effectively (33).

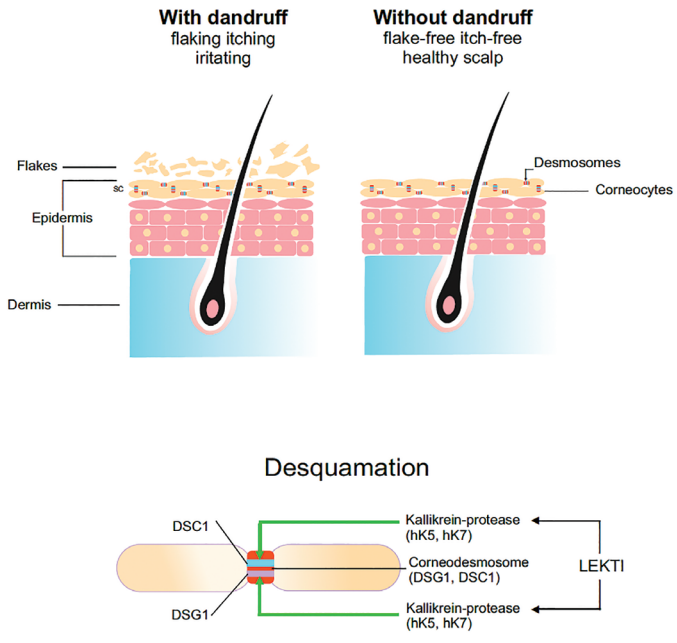


Figure 2 | The schematic pathway of the desquamation process.
DSG1 = desmoglein-1, DSC1 = desmocollin-1, hK = human kallikrein, LEKTI = lympho-epithelial Kazal-type-related inhibitor.

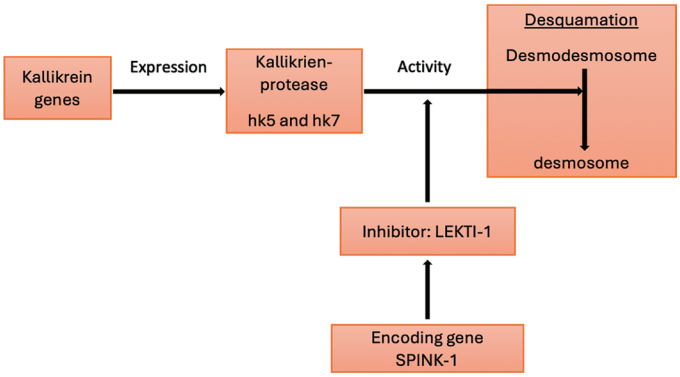


Figure 3 | The role of kallikrein proteases in desquamation of the stratum corneum.
SPINK = serine protease inhibitor Kazal-type, LEKTI = lympho-epithelial Kazal-type-related inhibitor, hK = human kallikrein.

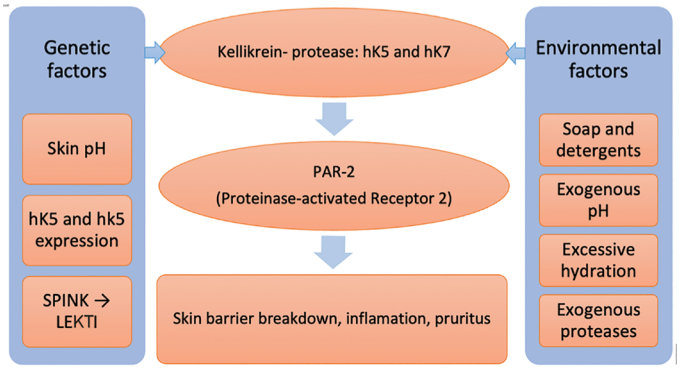


Figure 4 | The role of kallikrein protease and PAR2 in skin barrier breakdown.
PAR2 = protease-activated receptor-2, hK = human kallikrein, SPINK = serine protease inhibitor Kazal-type, LEKTI = lympho-epithelial Kazal-type-related inhibitor.

## The role of kallikrein protease inhibitor in flake formation

LEKTI is a precursor that undergoes rapid cleavage by furin, an endoprotease that activates the precursor proteolytically, producing a range of fragments. Each LEKTI fragment exhibits specific and distinct inhibitory effects on hK5 and hK7, forming a highly stable and irreversible binding complex (34). Several hK-specific pharmacological inhibitors have been developed to explore potential therapeutic applications (6, 35, 36).

The *SPINK5* gene encodes LEKTI, a serine protease inhibitor essential for regulating skin barrier formation (37). Defects in *SPINK5* can lead to severe disorders, such as Netherton syndrome, a genetic disorder characterized by abnormal keratinization. In *SPINK5* deficiency, protease hyperactivity disrupts the degradation of desmosomal proteins, resulting in markedly reduced levels of DSG1 and DSC1 in the outermost viable layers of the epidermis. This reduction is linked to the premature breakdown of corneodesmosomes. The activities of hK5 and hK7 drive this early

degradation of corneodesmosomal cadherins, which are transmembrane proteins essential for cell–cell adhesion. Expression of hK5 and hK7 persists in cell layers where DSG1 and DSC1 levels are diminished.

In cases with typical epidermal protease activity or residual LEKTI expression, normal cadherin levels are maintained, resulting in less severe disease symptoms (38). Mutations or defects in the *SPINK5* gene, contribute to excessive proteolysis in the SC. The degree of serine protease activation is positively correlated with barrier defects and clinical severity, and inversely correlated with residual LEKTI levels. Weakening of the SC is associated with heightened serine protease activity, corneodesmosome loss, and degradation of DSG1 and DSC1 (39). Increased KP activity plays a significant role in the pathogenesis of the disease. The actions of hK5 and hK7 influence the phenotype observed in *SPINK5* knockdown. Specifically, reducing the activity of hK5 or hK7 partially improves epidermal structure, leading to an increase in epidermal thickness and enhanced expression of DSC1, DSG1, and (pro)filaggrin.

Inhibiting hK5 and hK7 may offer therapeutic benefits for dandruff treatment (40). Herbal KP inhibitors present a promising avenue for developing new ingredients for dandruff treatment. These inhibitors are frequently incorporated into various herbal antidandruff shampoos (41). Notable examples include *Apium graveolens*, *Bauhinia bauhinioides*, and *Annona squamosa*. In addition, other plants may also contain KP inhibitors targeting hK5 and hK7, which could be further explored to create novel topical antidandruff agents. Several herbal materials of interest for their antidandruff properties include pomegranate seed oil (42), coffee (43), *Melaleuca alternifolia* leaf oil (44), the roots of *Asparagus racemosus* (45), *Azadirachta indica* leaves, and *Cinnamomum zeylanicum* (46). These plants contain various bioactive compounds, such as essential oils (46), phenolic compounds (43), and peptides (47).

*Apium graveolens* seed oil contains senkyunolide A (SENKY), a natural bioactive compound that, according to some studies, could have beneficial effects on epidermal function (48). SENKY (Fig. 5) can effectively control *Malassezia*, reduce dandruff, and soothe the scalp. It enhances the production of human β-defensin 2 (hBD2) in keratinocytes while inhibiting the production of interleukin-8, prostaglandin-E2 (PGE-2), toll-like receptor 9 (TLR-9), and sebum. Clinically, SENKY has been shown to significantly decrease dandruff severity, irritation, redness, and itching. It helps maintain scalp homeostasis by reinforcing barrier and defense functions, activating anti-inflammatory and detoxification pathways, and restricting the *Malassezia* niche (48). Consequently, SENKY may be a valuable treatment for dandruff-affected scalps, effectively reducing dandruff formation and promoting scalp comfort.

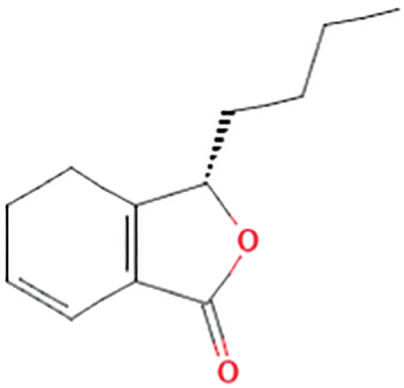


Figure 5 | Senkyunolide (SENKY).

*Bauhinia bauhinioides* seeds also contain a KP inhibitor. It is a potent inhibitor of human tissue KPs, particularly hK4 and hK7 (49). It is a single polypeptide chain (47) with potent anti-inflammatory and antioxidant properties (50). The seed of *Annona squamosa* (custard apple, Javanese local name: *srikaya*) is used for scalp lice and dandruff in traditional medicine (51). Its seed extracts have shown antioxidants and antipsoriatic properties (52, 53).

## The influence of sebum production on the activity of kallikrein protease

Adhesion proteins are essential for the formation and function of the SC and its barrier integrity, while intercellular lipids also play a critical role in scalp health (24). Scalp affected by oily dandruff is characterized by increased sebum levels, which contribute to a range of skin abnormalities. Both dry and oily dandruff conditions exhibit significantly reduced hydration, elevated pH, and increased transepidermal water loss (TEWL). However, dry dandruff tends to show even lower hydration levels compared to oily dandruff. In both types, hK5 levels are notably elevated, with higher concentrations found in oily dandruff. Additionally, the altered distribution of corneodesmosomes on corneocytes is especially pronounced in oily dandruff. Consequently, sebum levels should be considered when developing strategies to manage dandruff effectively (4).

Sebum production in the scalp is influenced by pH levels, which play a crucial role in lipid synthesis within the SC. The activity of enzymes involved in lipid synthesis is highly pH-dependent. When the pH environment shifts from acidic to alkaline, it inhibits metabolic pathways essential for regeneration and activates enzymes that promote desquamation, compromising the SC's barrier function (54). A lower skin pH is associated with the downregulation of the Na+/H+ antiporter (NHE1), and reduced NHE1 levels can lead to increased skin pH. This change results in defects in lipid enzymatic processing and delays the maturation of lamellar membranes. In contrast, compromised SC integrity is closely linked to elevated pH, which activates KPs, leading to the premature degradation of corneodesmosomes. Fortunately, these abnormal conditions can be normalized through acidification of the SC. Therefore, acidification therapies should be considered as a potential strategy in the treatment of dandruff (55).

## The influence of environmental factors on the activity of kallikrein protease

The skin and scalp epithelial barriers serve as the primary interfaces for maintaining a homeostatic balance between the host and the environment. These barriers constitute the first line of defense, offering protection against various environmental factors, including air pollution, chemical hazards (such as detergents, oxidative stress, water exposure, and UVB radiation), and biological threats such as *Malassezia* (56).

Detergents are known skin irritants that adversely affect keratinocytes. Exposure to detergents can lead to skin barrier defects, resulting in altered mRNA expression in keratinocytes and increased activity of enzymes that degrade corneodesmosomes (57). Furthermore, detergents can inactivate SCTE even at low concentrations (32). To counteract these effects, a commercial zinc pyrithione (ZPT) shampoo has been introduced to restore

the ultrastructure of the SC to normal while also addressing the underlying causes of dandruff (58). The use of ZPT shampoo can improve scalp conditions, as evidenced by a reduction in flaking, decreased epidermal thickness, lower levels of inflammatory biomarkers, and enhanced integrity of the epidermal barrier (59).

Oxidative stress arises when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them. This imbalance can have harmful effects on the scalp, leading to various negative consequences for its health (60).

In contrast to detergents, water exposure can promote the formation of amorphous intercellular lipids. Excessive water exposure can disrupt barrier lipids and intercellular lamellar bilayers, leading to increased permeability and susceptibility to irritants (61). To maintain skin moisture, the use of moisturizers is essential. Moisturizers help replenish intercellular lipid lamellae and form a hydrolipid film on the skin's surface, which preserves hydration and prevents TEWL (62).

UVB irradiation can increase the activity of hK5 and hK7, promoting desquamation (63). It upregulates the expression of these proteases while downregulating the expression of SPINK5. The activities of hK5 and hK7 are normally regulated by LEKTI, which is encoded by the *SPINK5* gene.

The presence of *Malassezia* and other skin microorganisms can be considered environmental stressors, particularly in the context of dandruff. *Malassezia*, recognized for its lipophilic properties, is commonly associated with dandruff development. Understanding the growth profile of *Malassezia* in the scalp of individuals with dandruff may offer new alternatives for prevention and treatment (64). Its distribution on the surface of the SC is uneven; they tend to cluster on certain corneocytes while leaving others almost free of them (65, 66). Antifungal agents alone are often ineffective in fully eliminating dandruff (67, 68). Currently, dandruff is considered a multifactorial condition influenced by microbial colonization and host factors, such as sebum production (69).

## Discussion

KPs have emerged as promising targets for pharmacological intervention in dandruff (70). Both activators and inhibitors of hKs hold therapeutic significance. Activators can help manage hyperkeratosis by promoting hK proteolysis, whereas inhibitors of overactive hKs in the epidermis are effective in addressing excessive skin desquamation (71).

Restoring the scalp barrier with moisturizers is a crucial component of dandruff treatment. Lifestyle modifications, including proper scalp care routines, also play a vital role. Additionally, patients with dandruff may benefit from pharmacological agents such as corticosteroids, calcineurin inhibitors, and phosphodiesterase 4 inhibitors, with combining them in a single formulation potentially improving efficacy and treatment outcomes (72).

The expression of active hKs in the scalp provides an opportunity to utilize proteolytically cleaved prodrugs for the localized release of active ingredients precisely at sites of hK activity. This highlights the need to explore and design alternative strategies for developing and testing hK-based therapeutics (71).

In a previous publication, we underscored the potential of incorporating lipase inhibitors, such as orlistat, to control *Malassezia* growth and sebum production. However, as *Malassezia* is not the sole factor in dandruff pathogenesis, protease inhibitors are equally essential. An enzyme inhibition-based treatment strategy could effectively promote a healthy scalp environment and reduce the likelihood of dandruff recurrence. Such an approach may minimize the reliance on ketoconazole-based shampoos. This paves the way for novel therapeutic concepts centered around "corneotherapy" and "corneocare," emphasizing the maintenance and repair of the SC barrier (29).

## Conclusions

Two KPs, hK5 and hK7, play a crucial role in maintaining a healthy scalp. Their overexpression and increased activity can lead to excessive desquamation, contributing to the development of dandruff. As new dandruff therapies are explored, KPs are anticipated to become key targets. Specific protease inhibitors, such as LEKTI, along with other protease inhibitors, may help reduce the activity of these KPs and mitigate dandruff symptoms.

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