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Original Research Article

Effectiveness of luliconazole vs ketoconazole topical formulation in reversing damaged hair cuticle

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ABSTRACT

Background : Azole antifungal agents are effective agents for treating scalp ailments such as seborrheic dermatitis. Luliconazole (LZ) is a new azole with unique effects against clinically important dermatomycotic fungi. This study examines the impact of different topical formulation of Luliconazole vs Ketoconazole (KZ) on damaged hair cuticle repair after 5 and 10 washes, using SEM images and sensory Analysis.

Materials and Methods : In this in-vitro study, twelve damaged hair tresses were divided into two groups, and treated with LZ and KZ formulations. Both groups underwent pretreatment with 20% Sodium Laureth sulfate (SLES) and damage induction using 9% H_2O_2 and 20% ammonium solution, followed by respective LZ (Lupizol ZS, manufactured by Lupin Ltd, India) and KZ therapies. SEM imaging and expert sensory analysis were conducted at baseline, after 5, and 10 washes to evaluate surface characterization like cuticle upliftment, smoothness, and softness.

Result: After five washes, LZ-treated hair exhibited smooth, intact cuticles with no upliftment, improving to grade 1 cuticle damage. In contrast, KZ-treated hair continued to show substantial upliftment without damage grade improvement. After ten washes, LZ maintained grade 1 damage and 0 μm upliftment, while KZ-treated strands persisted in showing considerable cuticular distress. Sensory analysis supported these results, with LZ improving hair smoothness and softness by 2.42x and 2.72x respectively, after ten washes, significantly outperforming KZ. Visually, LZ-treated hair appeared smoother and healthier, indicating its greater effectiveness in enhancing hair integrity post-washing.

Conclusion: The botanical conditioner-based formulation of LZ is more efficacious in enhancing hair integrity post-washing compared to the Ketoconazole formulation. Well-controlled human studies are required to further establish the clinical effects on human participants.

1. Introduction

The resilience and aesthetic quality of hair significantly depends on its mechanical properties, particularly the state of the cuticle. This outermost layer, formed by overlapping scales, acts as a shield for the hair's inner structure, playing a critical role in hair's durability, moisture preservation, and shine.[1,2] Damage to the cuticle, which can manifest as hair cuticle upliftment or detachment, compromises the hair shaft, leading to increased porosity and a greater likelihood of breakage. This condition is often exacerbated by environmental stress, harsh styling practices, and scalp disorders which can be marked by red, flaky, and itchy scalp, further impairing the hair's structural integrity.[3] Therefore, understanding the interaction between hair care products and the hair cuticle is paramount, especially in the context of treating scalp conditions that may contribute to cuticular damage.

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Azole antifungals, comprising imidazoles and triazoles, effectively treat various fungal infections. Imidazoles such as ketoconazole, clotrimazole, miconazole, and econazole were early developments in this class, while triazoles, including itraconazole and fluconazole, are newer generations offering broader activity and fewer side effects. Newer generation imidazole have also been developed which offer similar advantages like triazoles.[4–6]

Particularly in treating scalp conditions like seborrheic dermatitis and dandruff, both older and newer generations of imidazole's have proven efficacy. Ketoconazole, an imidazole, disrupts fungal cell membranes by inhibiting cytochrome P450 14α-demethylase (CYP51A1), a key enzyme in ergosterol synthesis leading to impaired fungal growth while luliconazole, newer generation imidazole, is believed to inhibit the enzyme lanosterol demethylase which is needed for the synthesis of ergosterol, thereby inhibiting the fungal growth.[5,7]

Scalp conditions such as seborrheic dermatitis and dandruff, are characterized by flaking, itching, and scalp inflammation that requires frequent use of prescribed medication. The use of antifungal imidazoles, particularly KZ shampoo, can lead to side effects such as pruritus, scalp and hair dryness, and application site reactions.[8] These negative impacts on hair cosmesis can pose challenges in patient compliance, especially when considering the treatment's effects on damaged hair. The chronic and recurring nature of dandruff necessitates ongoing use of these medicated shampoos for symptom management and flare-up prevention. Balancing efficacy with cosmetic side effects is crucial for ensuring patient adherence to the treatment regimen.[9]

Recognizing the need to maintain hair cosmesis while effectively treating dandruff has spurred the development of next-generation dandruff shampoos. These newer formulations involve the advantage of newer generation imidazole based on botanical conditioning that aim to mitigate the cosmetic side effects, such as hair damage and scalp irritation, while still providing robust antifungal action to manage dandruff symptoms effectively. Therefore, the current study compares the conditioning effect of two formulations of LZ and KZ, on hair health, providing essential insights for healthcare professionals.

2. Materials and Methods

2.1. Objective & study design

This research compares the effects of two haircare formulations on damaged hair tresses: a botanical conditioner-based Luliconazole 1% + salicylic acid 3% + Zinc pyrithione (ZPTO) 1% (test group) containing Tetearamidoethyl Diethonium Succinoyl Hydrolyzed Pea Protein, and Ketoconazole 2% + ZPTO 1% (comparator group). The study was conducted on a total of twelve tresses, with each group consisting of six. The primary objective was to compare the effects of LZ and KZ formulation on hair damage after 5 and 10 wash cycles, using SEM imaging for structural analysis and sensory assessment for evaluating hair smoothness and softness.

2.2. Procedure

3. Preparation of hair tresses

In the preparation phase of the study, twelve natural black hair tresses were selected, each weighing about 15-20 grams and measuring approximately 15-18 inches in length. To ensure uniformity, any knots found in these tresses were carefully combed out. These tresses were then washed using a 20% SLES solution, applying roughly 1 ml per tress, to effectively remove sebum and debris. Following the washing process, the tresses were thoroughly dried using a hair dryer.

4. Inducing Damage to Hair Tresses

The process of inducing damage to the hair tresses involved the preparation of a specific solution containing 9% Hydrogen Peroxide (H_2O_2), with the quantity doubled to account for its 50% activity, and 20% Ammonia Solution, based on a 25-28% active solution. The pH of this solution was maintained at around 10.5 to ensure consistency. The hair tresses were then immersed in this damaging solution for a duration of one hour. Following this immersion, the tresses underwent a thorough rinse for five minutes using 40°C distilled or tap water. This step was crucial for removing any residual ammonia and hydrogen peroxide from the hair. Finally, the tresses were towel-dried and gently combed to eliminate any loose hairs, completing the damage induction phase.

5. Hair Treatment, SEM Imaging, and Sensory Analysis

The procedure for evaluating hair softness and cuticle upliftment involves a series of steps. Initially, complete hair strands from all tresses were cut for SEM imaging. Followed by each tresses in the Test Group and Comparator Group is treated with 1ml of botanical conditioner based Luliconazole formulation (Luliconazole 1% + salicylic acid 3% + ZPTO 1%; Lupizol ZS, manufactured by Lupin Ltd, India) and Ketoconazole formulation (Ketoconazole 2% + ZPTO 1%), respectively. These tresses were then massaged for one minute and rinsed under tap water. After rinsing, the tresses were dried using the cold air setting of a hair dryer, completing one wash cycle. This process is repeated for a total of five wash cycles. Following these five washes, hair strands were again cut from each tress for SEM imaging. The washing steps (2 to 4) were then repeated for another five cycles, making it ten washes in total. After the tenth

wash, hair strands were once again cut from each tress for SEM imaging. Finally, the cuticle upliftment was evaluated through these SEM images, comparing the results between the Test and Comparator Group.

5.1. Measurements

5.2. Scanning electron microscopy (SEM Images)

Hair strands were cut from the tresses for SEM imaging at baseline, after 5 washes, and after 10 washes from both the LZ and KZ group. Hair samples were adhered to double-sided carbon conductive tape, mounted on aluminum stubs, and sputter-coated using platinum as the coating material (thickness: 10–20 nm). The coated hair specimens were then scanned using a SEM: (Model: Evo-18, Make- Zeiss India Ltd.) at an acceleration voltage of 15–20 kV. Multiple sections of each hair shaft were examined to confirm uniformity in the observed changes, ensuring they were not merely localized.

The damage assessment under SEM was performed via cuticle upliftment evaluation and, a five-grade system, as developed by Kim et al., 2010 was used to classify the extent of damage to the hair shaft.[10] The grading is as follows:

Grade	Interpretation
Grade 0	Represents virgin hair that is intact with a regular pattern of cuticle overlay.
Grade 1	Indicates hair with an irregular cuticle overlay but no visible cracks or holes.
Grade 2	Is characterized by significant cuticle lift, including cracks or holes, without the cortex being exposed.
Grade 3	Shows partial exposure of the hair's cortex.
Grade 4	Identified by the complete loss of the cortex.

5.3. Sensory Analysis

Smoothness and softness of the hair were evaluated by six experts using a 5-point scale, (0= Very rough, 1= rough, 2= neither rough nor smooth, 3= smooth, 4= Very smooth) at baseline, 5 washes and 10 washes.

5.4. Statistical Analysis

The statistical significance was measured at 95% confidence interval using unpaired t-test in SPSS version (v23.0)

6. Result

6.1. SEM images and cuticle repair

At baseline, SEM analysis of hair strands from both the LZ (Test) and KZ (Comparator) groups displayed notable cuticular disruption. Cuticle scales, typically aligned for protection, were perturbed with observable cracks, and some scales were raised from the shaft, indicative of a compromised state due to pretreatment with hydrogen peroxide. This resulted in a uniformly rough texture across both groups, consistent with Grade 3 cuticle damage (p=0.8845). (Table 1; Figure 11 A & B & Table 2)

Following five wash cycles, the KZ group's strands showed continued cuticle upliftment, with average measurements of 10.71 ±3.89 μm signifying substantial upliftment with no change in Cuticle damage grading. Conversely, the LZ group's strands exhibited cuticles that were comparatively smooth and intact, suggesting better maintenance of cuticular structure with cuticle upliftment value of 0 μm that is an indicative of less morphological impairment and a grade 1 cuticle damage (Table 1; Figure 1 C & D & Table 2)

Post ten washes, the KZ cohort's SEM images continued to reveal significant cuticular distress, evidenced by upliftment values of 09.54 ±4.95 μm and a discernible lack of cuticle reparation without any observed change in Cuticle damage grade. In contrast, the LZ cohort demonstrated notable improvements with cuticle upliftment values of 0 μm; the cuticles appeared less lifted and exhibited a smoother with a grade 1 cuticle damage, topography aligning more closely with the hair shaft—a reflection of healthier hair morphology. (Table 1; Figure 1 E & F & Table 2)

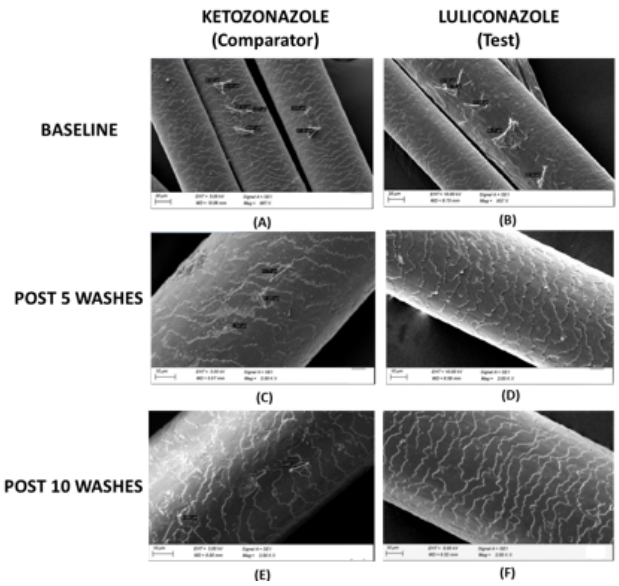

Figure 1: SEM micrographs of hair fibers treated with KZ and LZ shampoo: (A and B) hair fibers treated with 9% H_2O_2 and 20 % Ammonium solution. Hair Cuticle upliftment after (C&D) 5 washes and (E&F)10 washes.

Table 1: Comparative analysis of cuticle upliftment of KZ and LZ group

	KZ group (μm) (n=6)	LZ group (μm) (n=6)	p -value
Baseline	29.14 ±8.666 (μm)	28.81 ±8.86	0.798
5 Washes	10.71 ±3.89	0 (intact cuticle with no further distress)	<0.05
10 Washes	09.54 ±4.95	0 (intact cuticle with no further distress)	<0.05

Table 2: Comparative analysis of hair damage in KZ and LZ group

	KZ group (n=6)	LZ group (n=6)
Baseline	Grade 3	Grade 3
5 Washes	Grade 3	Grade 1
10 Washes	Grade 3	Grade 1

Note: KZ, Ketoconazole; LZ, Luliconazole

6.2. Sensory analysis of smoothness and softness of hair strands

In a study evaluating hair smoothness, LZ significantly enhanced smoothness after 5 and 10 wash cycles compared to the baseline, with the improvement being 2.42x (1.17 ± 0.41 to 2.83 ± 0.28) after 10 washes. KZ also showed improvement but to a lesser extent, at 1.51x (1.44 ± 0.50 to 2.17 ± 0.41) after 10 washes. While initial results after 5 washes indicated no significant difference between LZ and KZ, after 10 washes, LZ outperformed KZ with a 2.27x (1.66 ± 0.13 to 0.73 ± 0.09) greater improvement in smoothness. (Table 3; Figure 2)

Following 10 wash cycles, LZ demonstrated a 2.72x (1.00 ± 0.00 to 2.72 ± 0.44) increase in hair softness from the baseline, outperforming KZ, which showed a 1.82x (1.28 ± 0.33 to 2.33 ± 0.42) improvement. Although after 5 washes, LZ did not significantly exceed KZ in softness, by the 10th wash, it showed a substantially greater enhancement in softness with a 1.64x (1.72 ± 0.44 to 1.05 ± 0.09) better performance than KZ. (Table 4; Figure 2)

Hair Tresses treated with 9% H_2O_2 and 20 % Ammonium solution appeared frizzy, dry, and damaged with a rough texture and split ends, typical characteristics of hair that has been chemically treated or physically damaged. (Figure 2). The hair looks improved to some extent compared to the baseline damaged hair tresses, but still exhibits signs of frizz and some dryness after 10 washes with KZ. On the other hand, hair treated with LZ post 10 washes appears significantly smoother and healthier than the other two. This tress seems to have responded well to the LZ treatment, displaying less frizz and a smoother texture,

Table 3: Sensory analysis of smoothness

	Mean Score of Smoothness (Mean± SD)		p-value
	LZ group (n = 6)	KZ group (n = 6)	
Baseline	1.17 ± 0.41	1.44 ± 0.50	0.317
Post 5 wash cycles	1.94 ± 0.14	1.89 ± 0.27	
Post 10 wash cycles	2.83 ± 0.28	2.17 ± 0.41	
Mean diff (Post 5 wash cycles– Baseline) (p Value)	*0.77 ± 0.27 (0.001)	0.45 ± 0.23 (0.085) NS	0.209
Mean diff (Post 10 wash cycles– Baseline) (p Value)	*1.66 ± 0.13 (0.000)	*0.73 ± 0.09 (0.021)	*0.008

Note: * p-value <0.05 is considered to be statistically significant. KZ, Ketoconazole; LZ, Luliconazole

Table 4: Sensory Analysis of Softness

	Mean Score of Softness (Mean± SD)		p-value
	LZ group (n = 6)	KZ group (n = 6)	
Baseline	1.00 ± 0.00	1.28 ± 0.33	0.064
Post 5 wash cycles	1.78 ± 0.40	1.94 ± 0.53	
Post 10 wash cycles	2.72 ± 0.44	2.33 ± 0.42	
Mean diff (Post 5 wash cycles – Baseline) (p Value)	*0.78 ± 0.40 (0.000)	*0.66 ± 0.20 (0.026)	0.651
Mean diff (Post 10 wash cycles – Baseline) (p Value)	*1.72 ± 0.44 (0.000)	*1.05 ± 0.09 (0.000)	*0.048

Note: * p-value <0.05 is considered to be statistically significant. KZ, Ketoconazole; LZ, Luliconazole

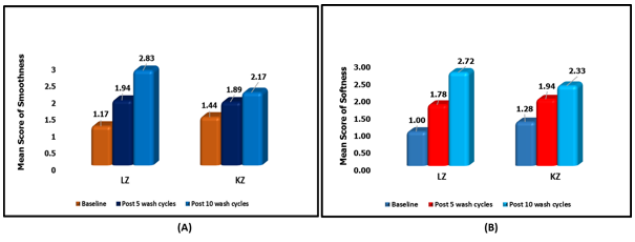

Figure 2: Sensory analysis of damaged hair strands treated with LZ and KZ: (**A**) Change in mean score of Smoothness (**B**) Change in means score of Softness.

indicating improved hair quality. (Figure 3)

These visual comparisons align with the previous discussion of the SEM and sensory analysis results. The photo evidence further supports the conclusion that LZ is more effective in repairing and maintaining hair cuticle integrity compared to KZ, particularly after repeated washing cycles, which could be due to LZ's unique properties that contribute to cuticle repair and maintenance.

Figure 3: Comparison of damaged hair tresses, treated with Ketoconazole, and treated with Luliconazole after 10 washes.

7. Discussion

This study presents a comparative analysis of the effects of Ketoconazole (KZ) and Luliconazole (LZ) formulations on the repair of hair cuticle damage induced by hydrogen peroxide and ammonium solution, with a particular focus on changes observed after repeated wash cycles. SEM analysis revealed that the initial damage observed in both KZ and LZ groups aligns with prior research indicating that hydrogen peroxide is a potent agent in hair cuticle damage, primarily through oxidative stress mechanisms.[11] This is consistent with our baseline observations of disrupted cuticle scales and a rough texture across both group in the current study.

After five washes, LZ-treated strands showed smooth, intact cuticles, with no cuticle upliftment, indicating less damage and a reduction to grade 1 cuticle damage, while KZ-treated strands continued to exhibit substantial upliftment with no improvement in damage grade. After ten washes, the LZ group maintained this improvement with 0 μm upliftment and sustained grade 1 damage, whereas KZ strands continue to showed notable cuticular distress and no cuticle damage grade improvement. Sensory analysis corroborated these findings, with LZ significantly improving hair smoothness and softness after ten washes, showing 2.42x and 2.72x greater improvement compared to KZ. Visually, LZ-treated hair appeared less frizzy and smoother, suggesting better repair and maintenance of hair quality, while KZ-treated hair still displayed signs of damage, supporting the conclusion that botanical conditioner-based formulation of LZ is more efficacious in enhancing hair integrity post-washing.

Ketoconazole (KZ) is well-known for its antifungal properties and its role in managing seborrheic dermatitis (SD). However, recent research, such as Heel et al., 2012 suggests that KZ may have limited effectiveness in hair cuticle repair.[12] In contrast, a study by Parasramani et al., 2022 comparing a Luliconazole (LZ) based shampoo, which also includes salicylic acid and zinc pyrithione, to a KZ-based shampoo, found the LZ formulation more effective in reducing the Seborrheic-Dermatitis-Severity-Score and improving overall hair health.[13]

The contrast between LZ and KZ extends to their side effects and cosmetic acceptability. KZ shampoos, while effective for certain conditions, have been linked to adverse effects such as itching, scalp and hair dryness, and in more severe cases, hair discoloration and contact dermatitis.[8,14] On the other hand, luliconazole, representing the newer generation of antifungal agents, stands out for its lower incidence of adverse effects, enhanced tolerability, and greater patient satisfaction.[13] This shift marks a significant advancement in dermatological treatments, positioning agents like luliconazole as preferable alternatives to traditional options like ketoconazole, especially considering their broader dermatological utility and improved patient experience.

The present LZ formulation's advantage is further enhanced by its inclusion of Tetearamidoethyl Diethonium Succinoyl Hydrolyzed Pea Protein, a botanical conditioner derived from vegetable peptides. This ingredient specifically targets damaged hair cuticles, aiding in restoring their barrier function and improving hair texture.

In addition, the present study adds to this field by using Scanning Electron Microscopy (SEM) to measure hair cuticle upliftment—a key indicator of shampoo conditioning effect—and sensory analysis for hair smoothness and softness. This comparative approach provides insights into the effects of LZ and KZ formulations on comprehensive hair health. Moreover, considering dandruff as a chronic scalp condition, effective treatment relies not only on symptom control but also on patient compliance linked to the cosmetic qualities of the shampoo pertaining to recurrent nature of the condition. In a double-blind cross-over study involving 40 women with mild to moderate dandruff, a 1% pyrithione zinc conditioning shampoo was preferred over a 2% ketoconazole shampoo for its better performance in hair-combing ease, smoothness, and reduced frizz/flyaway.[15] This preference underscores the importance of considering both therapeutic efficacy and cosmetic appeal in the development and selection of dermatological hair care products.

8. Conclusion

In conclusion, the findings of the present study highlight the superior performance of LZ-based botanical formulations in hair cuticle repair and maintenance, supporting LZ as a potential key ingredient in hair care products, particularly for chemically damaged hair. This study underscores the importance of considering both the dermatological efficacy and cosmetic impact of shampoos in the treatment of scalp conditions due to fungal infection.

9. Source of Funding

No external funding was received for this study.

10. Conflict of Interest

MK, VP and KP are salaried employees of Lupin limited.

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