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Effect of Cucumber (*Cucumis sativus*) Extract Cream on Aquaporin-3 and Hyaluronic Acid Levels in Wistar Rats with Xerosis Cutis

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Abstract

Background: Xerosis cutis is characterized by impaired barrier function and reduced hydration markers, including Aquaporin-3 (AQP3) and hyaluronic acid (HA). Cucumber extract (*Cucumis sativus)* contains antioxidants and humectants compounds that may improve skin hydration. This study investigated the effects of cucumber extract cream on AQP3 and HA levels in female Wistar rats (*Rattus norvegicus*) with grade II xerosis cutis.

Methods: This in vivo experimental study used a post-test-only control group design. Twenty-five female Wistar rats were randomly assigned into five groups: healthy control, xerosis control, positive control (10% ceramide), and treatment groups receiving 3% and 5% cucumber extract cream. Xerosis was induced by topical application of 70% acetone followed by 100% ethanol for 5–7 days until grade II xerosis developed. The creams were then applied topically for 14 days. AQP3 and HA levels were measured using enzyme-linked immunosorbent assay (ELISA).

Results: HA levels differed significantly among groups (p=0.016). The 5% cucumber extract cream-maintained HA levels comparable to healthy controls (611.25±248.61 vs. 685.26±194.95 ng/L; p=0.394). In contrast, ceramide and 3% cucumber treatments showed lower HA levels relative to healthy controls. AQP3 levels showed no statistically significant differences among groups (p=0.131), although descriptively higher expression was observed in the 5% cucumber-treated group.

Conclusions: Cucumber extract cream at 5% concentration helps maintain HA levels and shows a tendency to increase AQP3 expression, suggesting potential benefits for improving skin hydration in xerosis cutis and supporting skin health associated with aging.

Keywords: Aquaporin-3, cucumber extract cream, hyaluronic acid, xerosis cutis.

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Introduction

The use of cucumber (*Cucumis sativus*) extract has gained attention, particularly for addressing skin hydration issues.[1] Cucumber contains approximately 95% water, making it a potential natural hydrating agent.[2] Furthermore, it is rich in bioactive compounds such as flavonoids and vitamin C, which exhibit antioxidant and anti-inflammatory properties.[1] These characteristics make cucumber extract a promising candidate for managing dry skin conditions, including xerosis cutis.[3] However, despite its widely reported hydrating effects, there is limited evidence regarding its impact on molecular markers of skin hydration, such as Aquaporin-3 (AQP3) and hyaluronic acid (HA).

Xerosis cutis is a common dermatological condition characterized by impaired skin hydration and barrier dysfunction, particularly among the elderly population.[4] Clinically, xerosis cutis can be assessed using the Overall Dry Skin Score (ODS), which ranges from mild to severe and can be evaluated using a skin analyzer device.[5] Grade II xerosis is typically characterized by a rough, scaly skin with the presence of fine cracks.[6]

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Introduction

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The pathogenesis of xerosis cutis involves both external and internal factors. External factors include exposure to low humidity, cold environments, and chemical agents such as acetone and ethanol, while internal factors include intrinsic aging, structural and functional changes in the skin, systemic diseases, and medication use.[7,8] The pathogenesis of xerosis cutis involves both external and internal factors. External factors include exposure to low humidity, cold environments, and chemical agents such as acetone and ethanol, while internal factors include intrinsic aging, structural and functional changes in the skin, systemic diseases, and medication use.[9] Disruption of AQP3 function reduces water retention in the stratum corneum and increases trans epidermal water loss (TEWL), resulting in dry skin, reduced elasticity, and delayed barrier recover.[9]

In addition to AQP3, hyaluronic acid (HA) is important component in maintaining skin moisture. HA binds water molecules and helps retain hydration within the epidermis.[10] Decreased HA levels, often associated with oxidative stress, impair the skin's ability to maintain moisture balance and contribute to the development of xerosis cutis.[11]

Current management of xerosis cutis primarily involves the use of moisturizers, including humectants, occlusives, and emollients. However, conventional moisturizers may cause irritation or allergic reactions due to synthetic components such as propylene glycol, fragrances, and preservatives, as well as the oily texture of occlusive ingredients.[12,13] Moreover, the effectiveness of humectant-based moisturizers is often limited without an adequate occlusive agent, especially in low humidity environments, making them unable to prevent transepidermal water loss (TEWL).[6,14] Therefore, there is growing interest in natural alternatives with both hydrating and anti-inflammatory properties.

Furthermore, its active compounds exhibit anti-inflammatory properties that may alleviate erythema and skin irritation commonly associated with grade II xerosis cutis.[3] Therefore, in vivo models are required to assess the biological response of skin hydration markers within an intact epidermal barrier system. Female Wistar rats are commonly used in dermatological studies. due to their physiological relevance to human skin, particularly the role of estrogen in regulating skin metabolism, epidermal lipid production, and skin barrier restoration.[15–17] Thus, this study is to evaluated the effect of cucumber extract cream on AQP3 and HA levels in female Wistar rats with grade II xerosis cutis.

Methods

This experimental study used a post-test only control group design. All procedures received ethical clearance from the Animal Research Ethics Committee of the Faculty of Medicine, Universitas Islam Sultan Agung Semarang (No. 229/EC/KEPK-FK/IV/2025). The study complied with institutional guidelines for animal welfare, including humane handling, anesthesia prior to tissue collection, and minimal distress during experimentation.

A total of 25 healthy female rats, aged 10–12 weeks and weighing 200–250 grams, were used in this study. Prior to treatment, all animals underwent a seven-day acclimatization period at the Integrated Biomedical Laboratories, Faculty of Medicine, Universitas Islam Sultan Agung Semarang. During this period, the rats were maintained under controlled environmental conditions (temperature 20–26°C; humidity 50–60%) and were provided standard pellet feed and water ad libitum.

This study focused on grade II xerosis cutis due its high frequent enconterd in clinical and

is a critical threshold before progressing to a more severe form that involve inflammation and open wound.

The sample size was determined using the Federer formula to ensure adequate statistical power. The animals were randomly allocated into five groups (n=5 per group): a normal control group (K1) without xerosis induction, a negative control group (K2) induced with xerosis without treatment, a positive control group (K3) treated with 10% ceramide cream, and two treatment groups receiving cucumber extract cream at concentrations of 3% (K4) and 5% (K5). Randomization was performed using a simple random sampling method.

Grade II xerosis cutis was induced in groups K2 to K5 by applying a 1:1 mixture of 70% acetone and 100% ethanol to a 3×3 cm^2 area of shaved dorsal skin twice daily for up to seven consecutive days. Induction was discontinued once the ODS of 2 was achieved, characterized by visible scaling (small and moderate), pale skin, and mild surface roughness without signs of erythema.

Topical formulation was prepared by incorporating the cucumber extract at concentrations of 3% and 5% (w/w) into a standard cream base. The formulation composed of aqua, cetyl alcohol, stearyl alcohol, butylene glycol, glyceryl stearate, cetearyl alcohol, paraffinum liquidum, niacinamide, sodium lauryl sulfate, Aloe barbadensis leaf juice, tocopheryl acetate, bisabolol, phenoxyethanol, ceteareth-20, sodium cetearyl sulfate, BHT, sodium sulfite, citric acid, disodium EDTA, allantoin, hydrolyzed jojoba esters, ethylhexylglycerin, and sodium metabisulfite. All base ingredients were sourced from PT. Derma Elok Farma, whereas the cucumber extract was obtained from Mensa Group and analyzed for bioactive content. The base ingredients were heated to 70°C, homogenized, and cooled to below 40°C before the addition of cucumber extract to preserve its bioactivity. The final formulations were tested for homogeneity, pH (target 5.5–7.0), viscosity, spreadability, adhesiveness, and physical stability.

After xerosis induction, treatments were administered topically twice daily for 14 consecutive days using a standardized dose of 200 mg cream per rat. Skin hydration and surface morphology were assessed at three time points: after acclimatization (baseline), post-xerosis induction, and post-treatment, using a BW Boxy Skin® digital skin analyzer. Microscopic evaluation of the skin surface was also performed using a calibrated digital microscope to assess scaling, fissuring, and surface roughness.

On day 15, all animals were euthanized, and skin tissue samples from the treated area were collected for biochemical analysis. The levels of AQP3 and HA concentrations were quantified

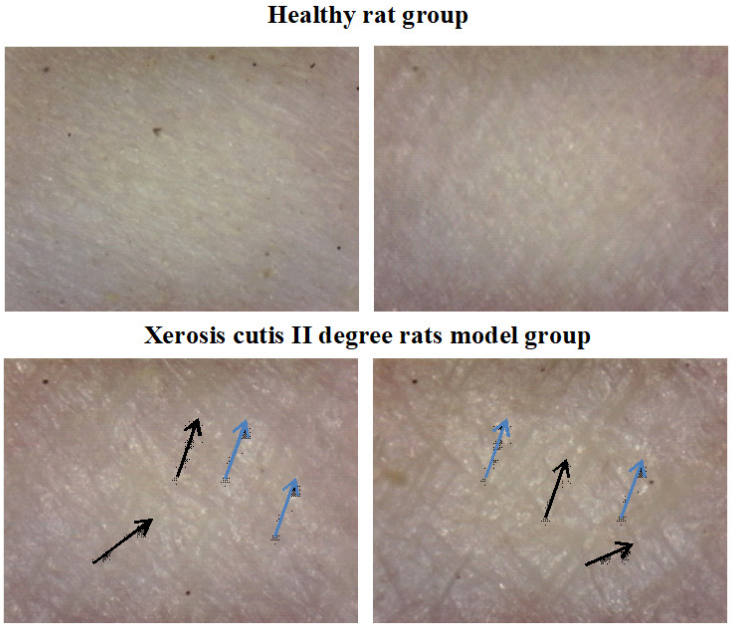

Figure 1 Macroscopic Appearance of Rat Skin in the Healthy Control Group and Grade II Xerosis Cutis Model

Table 1 Mean Hyaluronic Acid (HA) and Aquaporin-3 (AQP3) Levels Among Experimental Groups

Parameter	Group					p-value*
	Healthy	Xerosis (untreated)	Ceramide 10%	Cucumber 3%	Cucumber 5%	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Hyaluronic Acid (HA)	685.26 ± 194.95	648.89 ± 59.83	381.97 ± 76.54	479.68 ± 161.73	611.25 ± 248.61	0.016*
Aquaporin-3 (AQP3)	1665.0 ± 388.1	1753.1 ± 289.4	2093.8 ± 421.0	1448.6 ± 483.2	1725.0 ± 533.5	0.131

Note: Values are presented as mean ± standard deviation (SD). Statistical analysis was performed using the Kruskal–Wallis test. Statistically significant at $p<0.05$.

using enzyme-linked immunosorbent assay (ELISA). Tissue samples were homogenized in phosphate-buffered saline (PBS) containing protease inhibitors and centrifuged at 10,000 × g at 4°C. The supernatant was collected and added to microplates pre-coated with specific antibodies for AQP3 or HA. After incubation, tetramethylbenzidine (TMB) substrate was added for color development and absorbance was measured at 450 nm using a microplate reader. Concentrations were calculated against standard curves.

Statistical analysis was conducted using SPSS software. Data normality was assessed with the Shapiro-Wilk test, and homogeneity was evaluated using Levene's test. As the data were non-normally distributed, comparisons among groups were performed using the

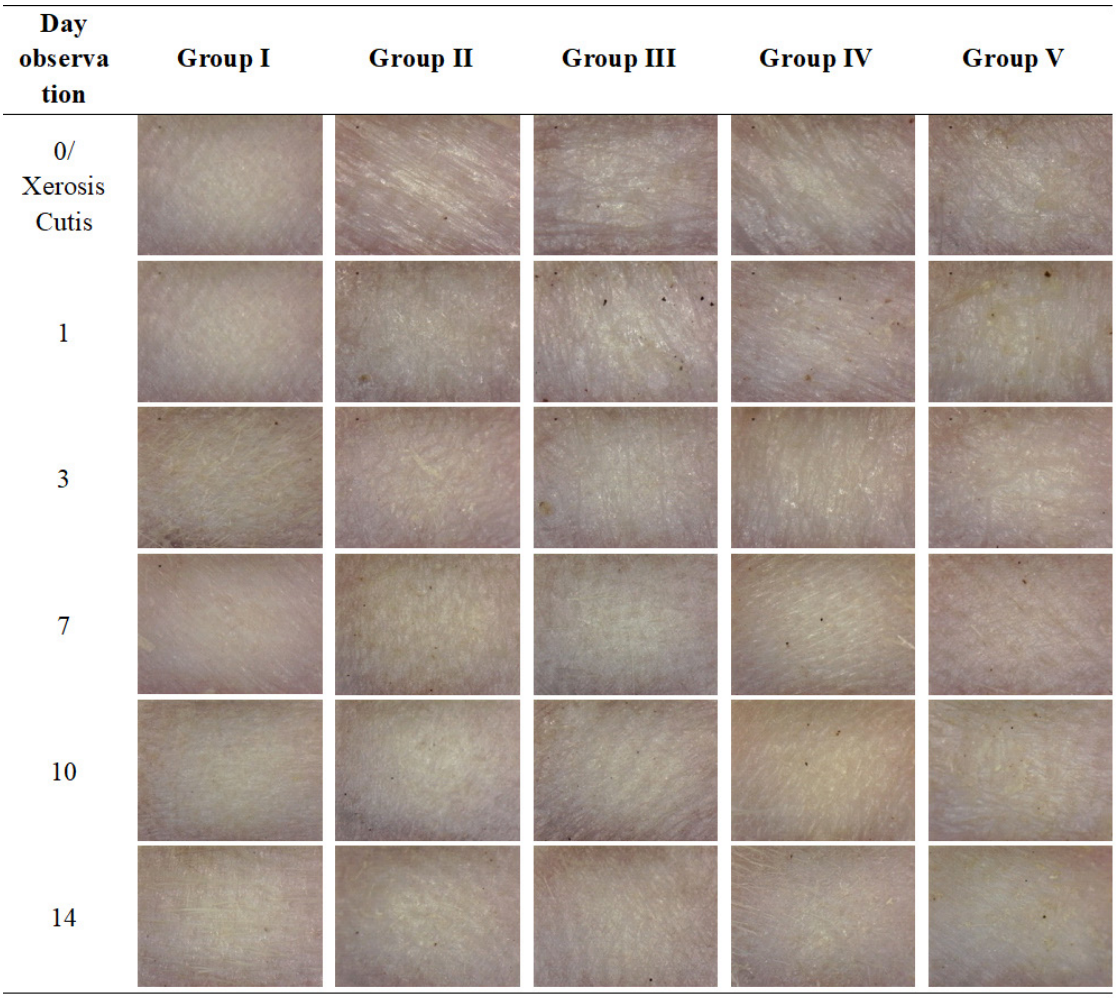

Figure 2 Macroscopic Changes in Rat Skin Observed Using Digital Microscopy on Days 1, 3, 7, 10, and 14 Across Experimental Groups

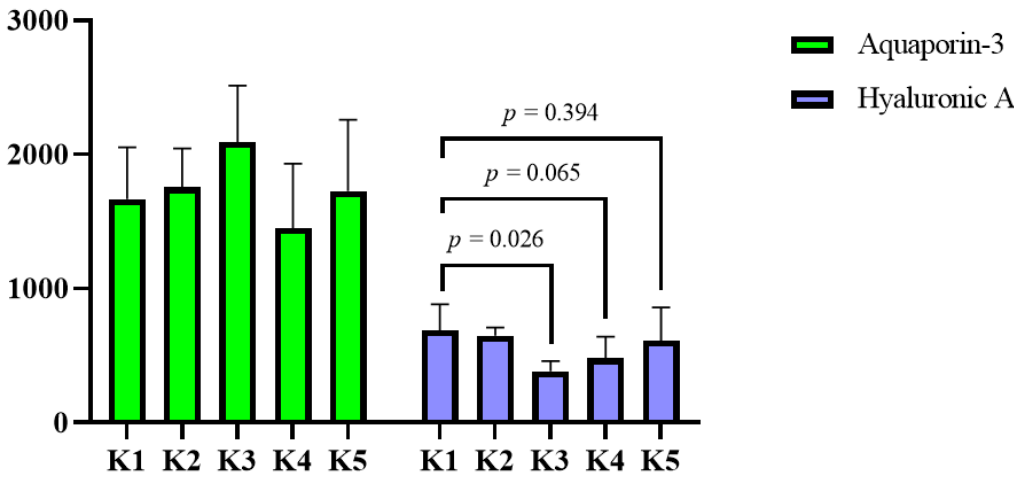

Figure 3 Mean Aquaporin-3 (AQP3) and Hyaluronic acid (HA) Levels in Rat Skin Tissue Across Experimental Groups.

Note: K1= healthy control; K2= xerosis without treatment; K3= ceramide 10% (positive control); K4= cucumber extract cream 3%; K5= cucumber extract cream 5%. Data are presented as mean ± standard deviation (SD). *p<0.05 indicates a statistically significant difference between groups.

Kruskal-Wallis test, followed by Mann-Whitney U tests for pairwise analysis. A p-value <0.05 was considered statistically significant.

Results

The results of this study demonstrate the effect of cucumber (*Cucumis sativus*) extract cream on skin hydration markers, namely Aquaporin-3 (AQP3) and hyaluronic acid (HA), in female Wistar rats with induced grade II xerosis cutis.

Validation of the xerosis cutis grade II model was performed through direct visual observation using a calibrated digital microscope. Skin morphology of normal rats was compared with that of rats following topical application of a 1:1 mixture of 70% acetone and 100% ethanol for seven consecutive days. The induced rats exhibited characteristic features of grade II xerosis, including visible scaling, pale skin appearance, and mild surface roughness without erythema (Figure 1).

In the healthy control group (K1), the dorsal skin appeared smooth, homogeneous, and uniformly pigmented, with no signs of dryness, fissures, or scaliness. The epidermal surface maintained structural integrity and adequate hydration. In contrast, rats in the xerosis cutis group (K2) exhibited visibly rough skin with uneven texture, whitish pallor, and fine to moderate scaling (black arrows), and superficial fissures (blue arrows). These features are consistent with moderate xerosis cutis (grade II), with no signs of erythema or hemorrhagic lesions, confirming appropriate model classification. The consistent morphological differences between groups support the reliability of this model for subsequent therapeutic evaluation.

Macroscopic evaluation of skin morphology was conducted on days 1, 3, 7, 10, and 14 using a digital microscope (Figure 2). On day 1, the K1 group showed normal, hydrated skin, and unaltered skin, whereas groups K2 to K5 exhibited dry, rough, and scaly skin following induction. By day 3, dryness and fissuring worsened in K2, while K3 (ceramide-treated group) began to show reduced scaling. The K4 group (3% cucumber extract) showed persistent scaling, whereas the K5 group (5% cucumber extract) demonstrated early improvement in skin moisture and surface smoothness

By day 7, K2 showed moderate scaling and visible superficial fissures, while K3 exhibited marked improvement. The K4 group still presented widespread scaling, whereas K5 showed further improvement with a more uniform skin surface. By day 10, dryness persisted in K2 with slight reduction in fissures, while K3 and K5 showed near-normal skin appearance. On day 14, K2 continued

to exhibit residual scaling and fissures, K4 remained coarse, and both K3 and K5 showed skin morphology comparable to the healthy group.

Biochemical analysis was performed on day 15 to evaluate AQP3 and HA levels using ELISA (Table 1). The highest mean AQP3 level was observed in the ceramide-treated group (2093.82 ± 421.01 ng/L), while the lowest was found in the 3% cucumber-treated group (1448.69 ± 483.22 ng/L). The 5% cucumber-treated group showed moderately increased AQP3 levels (1725.04 ± 533.59 ng/L), comparable to the healthy control group (1665.04 ± 388.15 ng/L).

In contrast, HA levels showed clearer differences among groups. The highest mean HA level was observed in the healthy control group (685.26 ± 194.95 ng/L), HA level was found in the ceramide-treated group (381.97 ± 76.54 ng/L), while the 3% cucumber-treated group showed intermediate values (479.68 ± 161.73 ng/L) (Table 1).

Normality testing revealed that AQP3 data in K1 were not normally distributed (p= 0.025), while other groups met normality assumptions. Variance homogeneity was confirmed (p= 0.389). The Kruskal–Wallis test showed no statistically significant difference in AQP3 levels among groups (p=0.131), although descriptive trends suggested higher AQP3 expression in the ceramide and 5% cucumber groups.

For HA, data from the 5% cucumber group were not normally distributed (p=0.034), and non-parametric analysis was applied. The Kruskal–Wallis test revealed a statistically significant difference among groups (p = 0.016). Post hoc Mann–Whitney analysis showed that HA levels in the 5% cucumber group were not significantly different from the healthy control group (p=0.394), but were significantly higher compared with the ceramide-treated group (p=0.026) and showed a borderline difference compared with the 3% cucumber group (p=0.065).

The 5% cucumber extract cream maintained HA levels close to those of the healthy control group (611.25 ± 248.61 vs. 685.26 ± 194.95 ng/L), with no statistically significant difference between these groups (p=0.394). In contrast, both the ceramide-treated group (381.97 ± 76.54 ng/L) and the 3% cucumber-treated group (479.68 ± 161.73 ng/L) showed lower HA levels compared to controls, with statistically significant or borderline differences (p=0.026 and p=0.065, respectively). These findings suggest that 5% cucumber extract cream has potential as a natural moisturizing agent by preserving HA levels (Figure 3).

Although AQP3 expression did not differ significantly among groups (p=0.131), descriptive analysis showed that the 5% cucumber-treated group had slightly higher levels (1725.04 ± 533.59 ng/L) compared to the healthy control group (1665.04 ± 388.15 ng/L), while the lowest levels were observed in the 3% cucumber-treated group (1448.69 ± 483.22 ng/L) (Figure 3).

Overall, graphical visualization demonstrated variation in both AQP3 and HA levels among groups, although differences in AQP3 were not statistically significant, consistent with the analytical findings.

Discussion

Macroscopic observations using a digital microscope revealed clear morphological differences between the healthy control group and the grade II xerosis cutis model group. These findings align with the clinical and visual criteria of grade II xerosis based on the ODS and are consistent with previous dermatological studies describing xerotic changes in experimental models.[18]

Following 14 days of treatment, the ceramide-treated group (K3) and the 5% cucumber extract group (K5) demonstrated the most prominent macroscopic improvements, characterized by reduced scaling and smoother, more hydrated skin. The 3% cucumber extract group (K4) also showed improvement, although less pronounced. These findings support previous studies indicating that ceramides function as effective occlusive agents, while cucumber extract exhibits humectant and antioxidant properties.[3] The present study extends these observations by demonstrating that clinical improvement is accompanied by preservation of hyaluronic acid (HA) levels, suggesting that cucumber extract may enhance skin hydration not only at the surface level but also through molecular mechanisms.

Aquaporin-3 (AQP3) is a membrane protein that facilitates the transport of water and glycerol and plays a critical role in maintaining epidermal hydration. Reduced AQP3 expression has been associated with xerosis cutis, impaired skin barrier function, and decreased elasticity.[19,20] In this study, the healthy control group showed stable AQP3 levels, reflecting normal skin physiology.

Interestingly, AQP3 levels in the untreated

xerosis group (K2) were slightly elevated compared to the healthy group, although this was not associated with clinical improvement. This finding may represent a compensatory response to barrier disruption induced by acetone–ethanol exposure. However, such compensation appears insufficient, possibly due to concurrent oxidative stress and inflammation that impair AQP3 function.[18]

The highest AQP3 levels were observed in the ceramide treated group (K3). suggesting that ceramides may enhance AQP3 expression in addition to restoring the lipid barrier. This effect may be mediated through activation of peroxisome proliferator-activated receptor gamma (PPAR-γ), which regulates epidermal differentiation and hydration pathways.[21]

In contrast, the 3% cucumber extract group (K4) showed the lowest AQP3 levels, while the 5% group (K5) demonstrated higher levels, approaching those of the untreated xerosis group. This pattern suggests a dose-dependent trend, potentially attributable to bioactive compounds such as vitamin C and polyphenols, which may support epidermal protein synthesis and reduce oxidative stress.[22]

Despite these trends, no statistically significant differences in AQP3 levels were observed among groups. This may be explained by the timing of tissue collection on day 14, which likely occurred after the peak expression phase of AQP3. Previous studies have shown that AQP3 expression typically increases during the early phase of skin repair (days 3–7) and subsequently declines as homeostasis is restored.[9,22,23] Therefore, the absence of significant differences may reflect a temporal limitation rather than a lack of biological effect.

Previous studies have shown that AQP3 expression increases significantly during the first 3–7 days of topical moisturizer application (e.g., ceramide), then decreases as homeostasis is reestablished.[24] Thus, it is plausible that any earlier upregulation had already subsided, resulting in non-significant intergroup differences.

Therefore, the absence of significant differences may reflect a temporal limitation rather than a lack of biological effect.[25] In this study, the highest HA levels were observed in the healthy control group, reflecting intact skin structure and balanced synthesis–degradation processes.

In the untreated xerosis group (K2), HA levels were only slightly reduced compared to the healthy group. This modest decline may indicate an early-stage response to skin barrier disruption, where structural damage impairs water retention despite relatively preserved HA levels.[26]

Treatment with 3% cucumber extract (K4) resulted in moderate increases in HA levels, suggesting that even low concentrations of bioactive compounds may begin to influence HA metabolism. The 5% cucumber extract group (K5) demonstrated the highest HA levels among treatment groups, approaching those of the healthy control. This finding supports the hypothesis that higher concentrations of cucumber extract enhance hyaluronan synthase activity while inhibiting hyaluronidase-mediated degradation.[26,27]

These results indicate that cucumber extract, particularly at a 5% concentration, may improve skin hydration primarily through HA-dependent mechanisms. The combined humectant and antioxidant properties of cucumber-derived compounds likely contribute to this effect.

Several limitations should be considered. First, the study involved a relatively small sample size and was conducted in an animal model, which may limit generalizability to human skin. Second, the evaluation was restricted to AQP3 and HA as hydration markers without including histological or additional biochemical parameters. Third, a base formulation control group was not included, making it difficult to exclude the potential effects of the cream base. Future studies should incorporate larger sample sizes, additional biomarkers, histological analysis, and earlier observation time points (particularly days 3–7) to better capture dynamic changes in AQP3 expression.

In conclusion, topical application of cucumber (*Cucumis sativus*) extract cream does not effectively increase AQP3 levels in female Wistar rats with grade II xerosis cutis, even though a trend toward increased expression is observed. However, the extract significantly increases hyaluronic acid (HA) levels, with values approaching those of the healthy control group. Notably, the 5% formulation demonstrates greater efficacy than the 3% formulation, suggesting a dose-dependent effect. These findings indicate that cucumber extract cream has potential as a topical agent for improving skin hydration in xerotic conditions.

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Author's Contributions

ADS contributed to the study conceptualization, study design, data collection, data analysis, and drafting of the manuscript. PH contributed to the study design, supervision of the research process, and interpretation of the data. STZ contributed to supervision, critical revision of the manuscript, and provided important intellectual input. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflict of Interest

The authors declare no conflicts of interest.

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Generative AI Disclosure Statement

The authors used ChatGPT (version 5.0; OpenAI) as an AI-assisted writing tool during manuscript preparation and to improve grammar, clarity, readability. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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