Original

Appl. Cosmetic Sci. & Tech. 1 (1): 74–81

Ganoderma lucidum Extract Improves Chronic Stress-Induced Impairment in Skin Barrier Function

Shota Hayashi*, Hiroyasu Iwahashi, and Akinori Kiso

Research Center, Maruzen Pharmaceuticals Co., Ltd., Hiroshima, Japan

The relationship between mental stress and skin disorders is well known, with cortisol as a contributing factor. Cortisol, a hormone vital for maintaining bodily homeostasis, may have different effects on the skin depending on whether its levels are temporarily elevated due to circadian rhythms or transient stress, or continuously elevated due to chronic stress. To understand the link between mental stress and skin disorders, it is crucial to assess the impact of cortisol on the skin under various stress states. However, it remains unclear whether the skin damage from chronic stress is driven by sustained high cortisol levels or by frequent fluctuations in cortisol. This study investigated the effect of cortisol on the ability of normal human epidermal keratinocytes to form tight junctions by varying cortisol exposure frequency. The results showed that transepithelial electrical resistance and claudin expression were reduced in cells continuously treated with cortisol, compared to those transiently treated with cortisol before differentiation induction. This difference was attributed to variations in the messenger RNA expression levels of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which converts inactive cortisone to active cortisol, and 11β-HSD2, which converts cortisol to cortisone between the 2 cell types, suggesting that the adverse effects of cortisol may be amplified in cells continuously exposed to cortisol due to increased expression of 11β-HSD1. Furthermore, we also established for the first time that *Ganoderma lucidum* (reishi mushroom) extract acts as an inhibitor of cortisone-to-cortisol metabolism, and alongside its component ganoderic acid A, mitigates the negative effects of continuous cortisol treatment on tight junction formation. Therefore, *G. lucidum* extract is anticipated to improve the decline in skin barrier function associated with chronic stress.

Key words: mental stress, chronic stress, temporary stress, cortisol, 11β-hydroxysteroid dehydrogenase type 1, 11β-hydroxysteroid dehydrogenase type 2, barrier function, tight junction, *Ganoderma lucidum* extract, ganoderic acid A, epidermal keratinocytes

1. Introduction

Cortisol, a hormone secreted by the adrenal cortex, plays a crucial role in maintaining physiological balance by increasing blood pressure, promoting gluconeogenesis in the liver, and suppressing inflammation.[1)] It is often referred to as a stress hormone owing to its elevated secretion in response to physical and mental stress.[2)] Prolonged cortisol

Received: October 4, 2024; Accepted: January 15, 2025

*Corresponding author: Shota Hayashi (E-mail: s-hayashi@maruzenpcy.co.jp)

Research Center, Maruzen Pharmaceuticals Co., Ltd., 1089-8 Sagata, Shin-ichi, Fukuyama, Hiroshima 729-3102, Japan

DOI: 10.69336/acst.2024-10

elevation resulting from excessive stress is associated with high blood pressure,[3] obesity,[4] and a weakened immune system.[5]

Mental stress is often associated with adverse effects on the skin, such as rough skin, eczema, and acne.[6] The skin's structure, which serves as a protective barrier against external factors, is composed of the stratum corneum, which provides a physical barrier, and the granular layer, which provides a biological barrier through tight junctions (TJs). Cortisol weakens this barrier function, contributing to stress-induced skin roughness.[7] However, cortisol is secreted in alignment with the circadian rhythm, causing the skin to experience temporarily elevated levels daily. Thus, it remains unclear whether the adverse effects of chronic stress on the skin are primarily due to high cortisol concentrations or frequent elevations.

This study aimed to reveal the underlying cause of cortisol-induced rough skin associated with chronic stress and identify substances that can address this mechanism. We assessed the impact of varying cortisol exposure frequency on TJ formation and the expression of cortisol-metabolizing enzymes in epidermal keratinocytes. Additionally, we investigated the effects of an extract from *Ganoderma lucidum* (reishi mushroom),[8] and its component, ganoderic acid A,[9] on TJ formation under cortisol influence, given the traditional use of the mushroom as a tonic, sedative, and treatment for chronic stress-related symptoms, such as neurasthenia and insomnia.

2. Materials and Methods

2.1. Cell culture

Normal human neonatal epidermal keratinocytes (NHEKs, Kurabo Industries, Osaka, Japan) were cultured at 37°C with 5% CO_2 in a growth additive-supplemented (0.67 μg/mL hydrocortisone [HC; cortisol], 10 μg/mL insulin, 0.1 ng/mL human epidermal growth factor, 0.4% bovine pituitary extract, 50 μg/mL gentamicin, and 50 ng/mL amphotericin B) medium (keratinocyte glowth mediume (KGM), Kurabo Industries) based on normal human epidermal keratinocyte basal medium (KBM, Kurabo Industries). Differentiation was induced using KGM without HC (KGM-HC) supplemented with 1.5 mM $CaCl_2$.

2.2. Cell stress induction

NHEKs were washed 2 times with phosphate-buffered saline (PBS) and then cultured in KGM-HC with or without 20 μM cortisol. Cells exposed to cortisol every 3 d were labeled "temporarily stressed cells (TSCs)," those treated with cortisol daily were labeled "chronically stressed cells (CSCs)," and cells not treated with cortisol were labeled "non-stressed cells (NSCs)."

2.3. Test substance

The fruiting bodies of reishi mushrooms were extracted with hot water, filtered, concentrated under reduced pressure, and freeze-dried to obtain the *G. lucidum* extract used in this study. Ganoderic acid A was purchased from Cayman Chemical (MI, USA).

2.4. Assessment of barrier function in the presence of cortisol

2.4.1. Assessment of epidermal intercellular barrier function

Cells subjected to stress induction for 3 d were seeded at 1.5×10^6 cells/well in a Transwell 12-well plate (Costar, NY, USA), and further stressed for an additional 3 d. Subsequently, differentiation was induced in a medium with or without 20 μM cortisol, and transepithelial electrical resistance (TEER) was measured using a Millicell-ERS (Millipore, MA, USA). TEER measurements were recorded every 24 h from differentiation induction initiation for 72 h without changing the medium during this period. Test substances were treated concurrently with the initiation of differentiation.

2.4.2. Immunostaining of TJ-associated proteins

Cells subjected to stress induction for 3 d were seeded at 1.5×10^4 cells/well on CELLview 10-well slides (Greiner, IL, USA) and underwent an additional 3 d of stress. Thereafter, the differentiation medium was replaced with 20 μM cortisol, and the cells were cultured for 24 h. Test substances were treated concurrently with the initiation of differentiation. Cells were subsequently fixed with ethanol/acetone and washed with PBS. Blocking was performed with 1% bovine serum albumin at room temperature (20°C–25°C) for 1 h, followed by washing with PBS. The cells were incubated for 18 h in a cool (4°C), dark environment with anti-claudin-1 (CLDN-1) antibody (Invitrogen, MA, USA) and anti-CLDN-4 antibody (Invitrogen). Thereafter, cells were washed 3 times with PBS containing 0.05% Tween-20 (PBS-T). Alexa Fluor 594-labeled secondary antibody (Invitrogen) and Hoechst 33342 (Dojindo Laboratories, Kumamoto, Japan) were added to cells and incubated for 30 min in the dark at room temperature. After 3 additional washes with PBS-T, the cells were photographed using a fluorescence microscope (Keyence, Osaka, Japan).

2.5. Evaluation of cortisol metabolic enzyme gene expression

NHEKs were seeded at 7.5 × 10^4 cells/well in a 24-well plate (Falcon, AZ, USA) and cultured for 18 h. Following 2 washes with PBS, cells were cultured in KGM-HC with or without 20 μM cortisol for 3 d. Thereafter, total RNA was extracted using ISOGEN II (Nippon Gene, Tokyo, Japan).

Total RNA was used to measure messenger RNA (mRNA) expression levels of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), 11β-HSD2, and the internal standard glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Detection was performed using a 2-step reverse transcription PCR with the Thermal Cycler Dice Real Time System III (Takara Bio, Shiga, Japan), employing PrimeScript RT Master Mix (Takara Bio) and TB Green Fast qPCR Mix (Takara Bio). Target mRNA expression levels were normalized to GAPDH mRNA expression. Primers for 11β-HSD1 and GAPDH were obtained from Takara Bio, and the primers for 11β-HSD2 are as follows:[10)]

11β-HSD2 Forward: gtcaaggtcagcatcatcca

Reverse: cactgacccacgtttctcac

2.6. Measurement of cortisol conversion

NHEKs were seeded at 5.0 × 10^4 cells/well on a 24-well collagen-coated plate (Iwaki, Shizuoka, Japan) and cultured for 18 h. After 2 washes with PBS, the test samples with KBM containing 1 μM cortisone were added, and the cells were cultured for 24 h. Thereafter, cortisol levels in the cell supernatant were measured using the Cortisol Parameter Assay Kit (R&D Systems, MN, USA).[11)]

2.7 Statistical tests

Values are expressed as the mean ± standard error (S.E.). Statistical significance was assessed using Student's t-test for comparisons between 2 groups, and Dunnett's test or Tukey's test for comparisons among 3 or more groups, with $p < 0.05$ considered statistically significant.

3. Results

3.1. The effect of cortisol on barrier function

3.1.1. Measurement of electrical resistance

To evaluate the impact of stress-induced cortisol on skin barrier function, cortisol was administered during NHEK differentiation, and TEER was measured as an indicator of epidermal intercellular barrier function. Additionally, the effects of varying cortisol treatment frequencies before differentiation induction were assessed. As shown in Fig. 1, in NSCs not treated with cortisol before differentiation, cortisol treatment during differentiation induction significantly reduced the increase in TEER compared to untreated controls ($p < 0.05$). TSCs, which were temporarily treated with cortisol before differentiation, showed similar TEER changes to NSCs up to 48 h after induction. However, TEER in TSCs was significantly higher than that in cortisol-treated NSCs after 72 h ($p < 0.05$). Conversely, CSCs continuously treated with cortisol before differentiation induction exhibited significantly suppressed TEER increases across all time points.

3.2.2. Effect on TJ formation

To assess the impact on TJs, which form intercellular barriers, we performed immunostaining to evaluate the production and localization of the TJ proteins CLDN1 and CLDN4. The results indicated that the fluorescence intensity around CSCs for both CLDN1 (Fig. 2A) and CLDN4 (Fig. 2B) was lower than that around cells subjected to other stress conditions. This finding confirmed that continuous cortisol treatment markedly inhibits TJ formation.

3.2. Changes in gene expression of cortisol metabolic enzymes

We evaluated the impact of different cortisol treatment frequencies on the mRNA expression of 11β-HSD1 and 11β-HSD2, enzymes involved in cortisol metabolism. In NHEKs treated with cortisol once and cultured for 72 h, 11β-HSD2 mRNA expression was significantly higher than that of untreated NHEKs ($p < 0.01$) (Fig. 3A). Conversely, NHEKs treated with cortisol 3 times at 24-h intervals and cultured for 72 h showed no increase in 11β-HSD2 mRNA expression; however, the 11β-HSD1 mRNA expression was significantly elevated compared to that of untreated NHEKs ($p < 0.01$) (Fig. 3B).

3.3. Reducing cortisol levels with *G. lucidum* extract

To identify substances that counteract cortisol's adverse effects on skin barrier formation, we assessed the impact of reducing cortisol levels in cells. Cortisone was added to NHEKs, and the amount of cortisol metabolized and released into the culture supernatant was measured. As shown in Fig. 4, it was confirmed that *G. lucidum* extract effectively reduces cortisol levels.

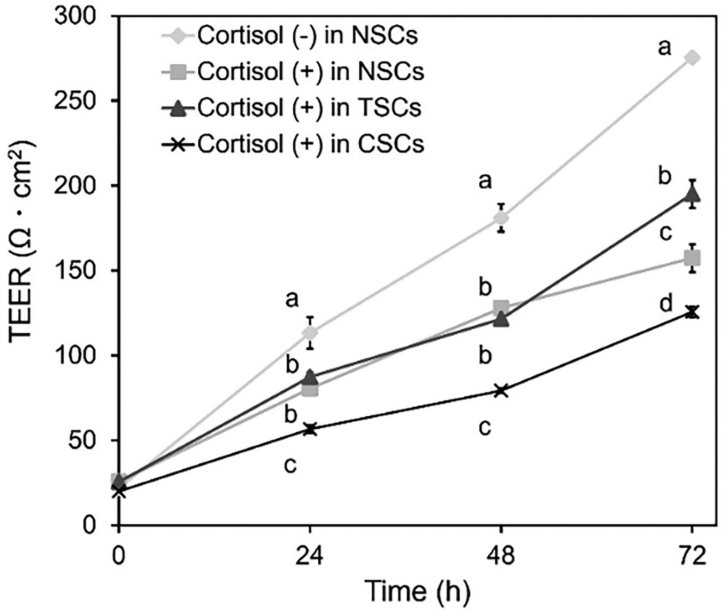

Fig. 1 Evaluation of barrier function under different cortisol treatment conditions. Differentiation in each stress model was induced by adding 1.5 mM $CaCl_2$ with either 0 or 20 μM cortisol. TEER was measured up to 72 h. Data are presented as the mean ± S.E., n = 3. Different letters (a, b, c, or d) indicate significant differences ($p < 0.05$) at each time point, using Tukey's test.

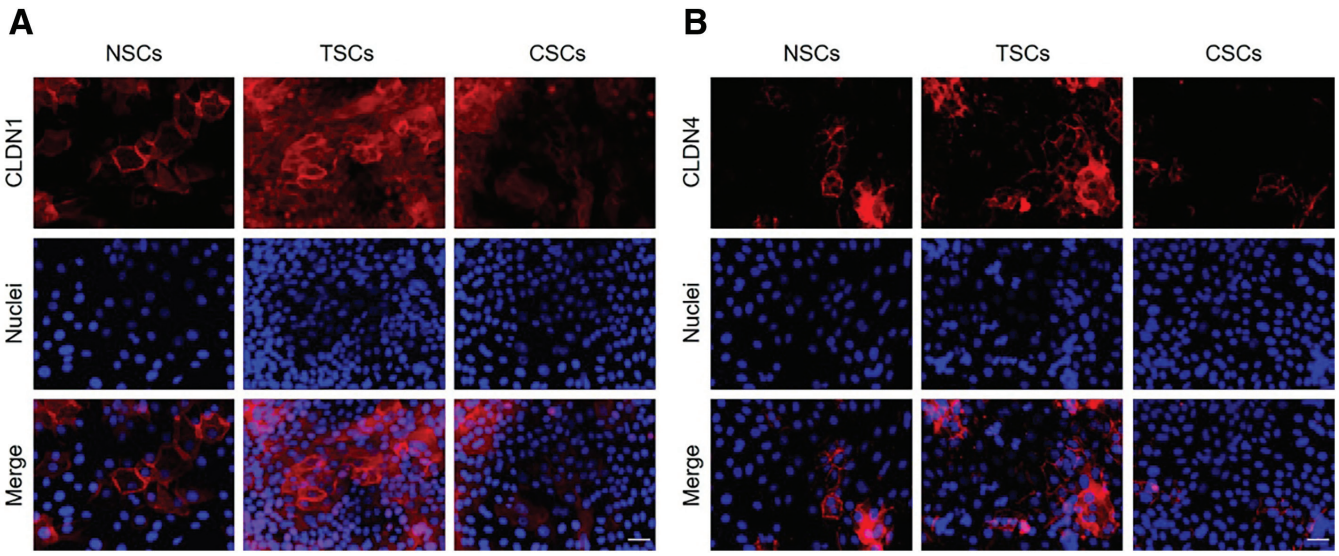

Fig. 2 Immunofluorescence staining of CLDN1 and CLDN4 under different cortisol treatment conditions. Differentiation in each stress model was induced using 1.5 mM $CaCl_2$ in the presence of 20 μM cortisol, with an incubation period of 24 h. The expression of CLDN1 (A) and CLDN4 (B) in the cells cultured under designated conditions was visualized using immunostaining. Nuclei were counterstained with Hoechst 33342. Scale bar = 40 μm.

3.4. Effect of *G. lucidum* extract on improving barrier function in chronic stress models

To determine whether *G. lucidum* extract, which is capable of reducing cortisol levels, mitigates the decline in barrier function caused by chronic stress, we investigated its effects, along with its component ganoderic acid A, on the reduction in barrier function observed in CSCs.

Treatment of CSCs with *G. lucidum* extract and ganoderic acid A significantly improved TEER reduction compared to that of CSCs without the test substances ($p < 0.05$) (Fig. 5). Additionally, an increase in pericellular fluorescence for CLDN1 (Fig. 6A) and CLDN4 (Fig. 6B) was observed, confirming the suppression of cortisol's adverse effects in CSCs.

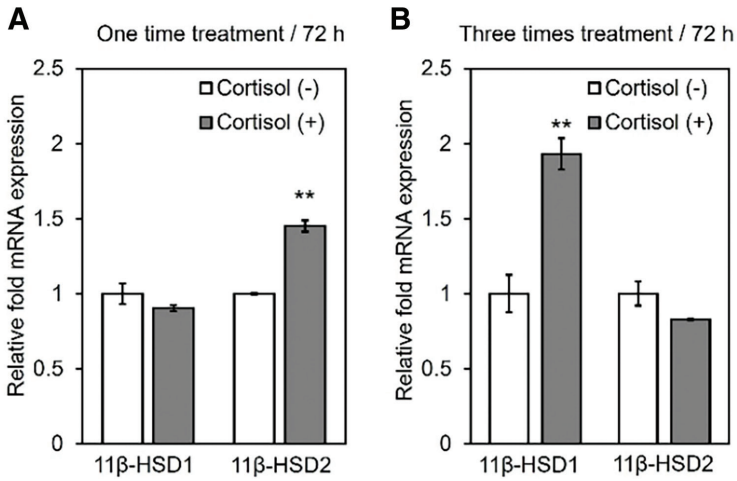

Fig. 3 Effect of cortisol on 11β-HSD1 and 11β-HSD2 mRNA expression levels in NHEKs under different cortisol treatment conditions. NHEKs were treated with 20 μM cortisol either once or every 24 h, followed by an incubation for 72 h. mRNA expression levels of 11β-HSD1 and 11β-HSD2 were analyzed via reverse transcription real-time quantitative PCR, and data are expressed relative to untreated NHEKs. (A) NHEKs were treated with 20 μM cortisol once and subsequently cultured for 72 h. (B) NHEKs were treated with 20 μM cortisol every 24 h and subsequently cultured for 72 h. Data are expressed as the mean ± S.E., n = 3, $^{**}p < 0.01$, using Student's t-test.

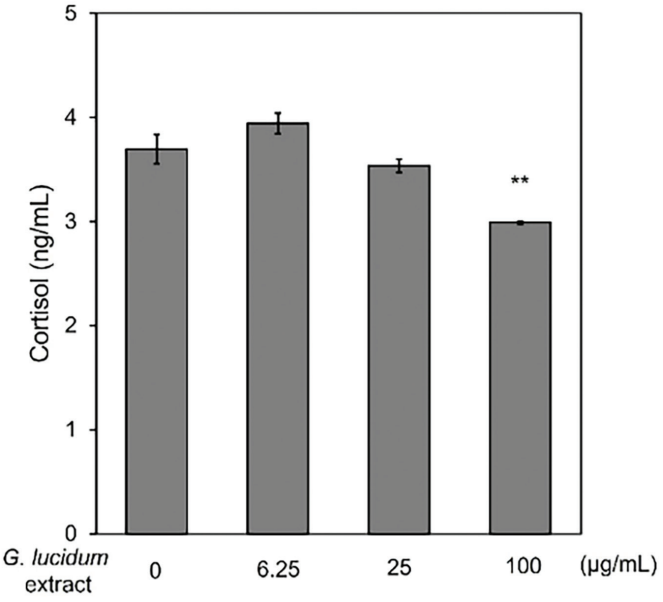

Fig. 4 Effect of *Ganoderma lucidum* extract on converting cortisone to cortisol. NHEKs were treated with 1 μM cortisone and *G. lucidum* extract. The cortisol levels in the cultured medium supernatant were determined using an enzyme-linked immunosorbent assay after 24 h. Data are presented as the mean ± S.E., n = 3, $^{**}p < 0.01$, *versus* control using Dunnett's test.

4. Discussion

Cortisol is released through the activation of the hypothalamus–anterior pituitary–adrenal cortex axis (HPA axis) in response to physical and mental stress and is known as the stress hormone.[12] It manages temporary stress by elevating blood pressure, blood glucose, and regulating metabolism.[1] Cortisol is also essential for maintaining homeostasis, promoting wakefulness, with levels rising from the late sleep stage to just before waking and gradually decreasing thereafter.[13]

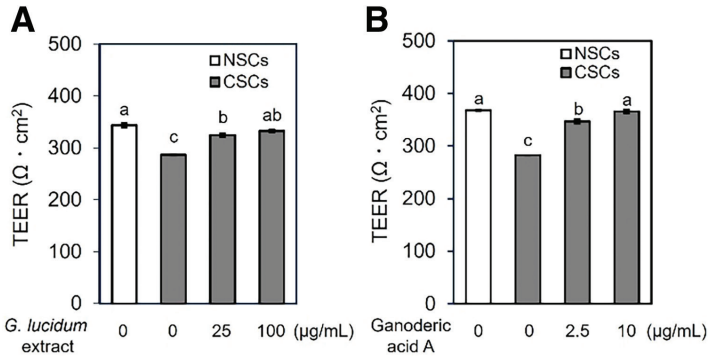

Fig. 5 Effects of *Ganoderma lucidum* extract and ganoderic acid A on barrier function in CSCs induced to differentiate in the presence of cortisol. NSCs and CSCs were induced to differentiate by adding 1.5 mM $CaCl_2$ under 20 μM cortisol. At the same time of differentiation, CSCs were treated with 0, 25, or 100 μg/mL *G. lucidum* extract (A) or 0, 2.5, or 10 μg/mL ganoderic acid A (B). TEER was measured at 72 h. Data are presented as the mean ± S.E., n = 3, with different letters (A, B, or C) indicating significant differences ($p < 0.05$) at each given time point, using Tukey's test.

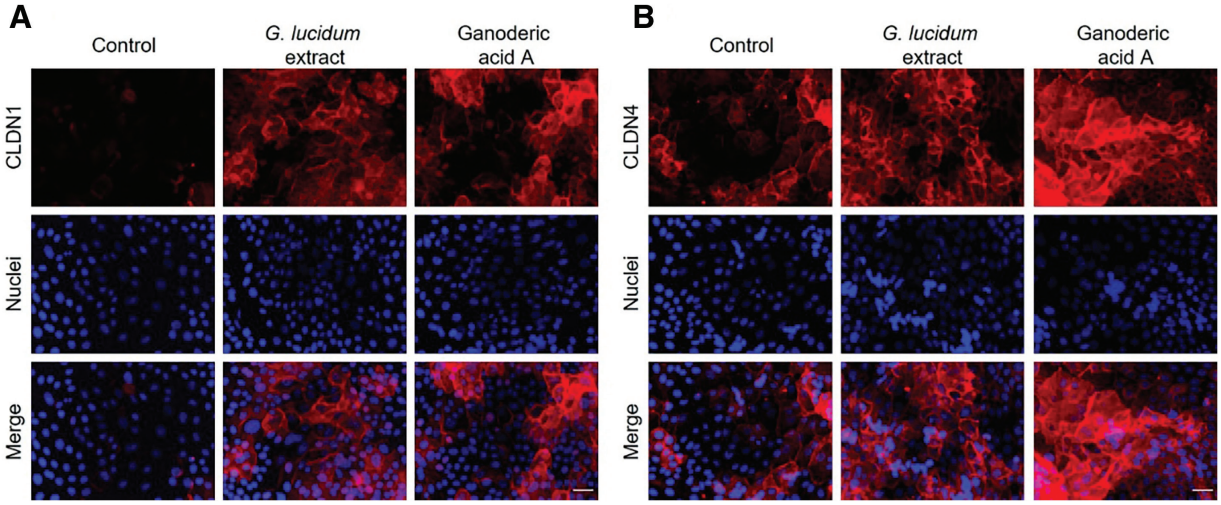

Fig. 6 Effects of *Ganoderma lucidum* extract and ganoderic acid A on CLDN1 and CLDN4 expression in CSCs induced to differentiate in the presence of cortisol. CSCs were treated with 100 μg/mL *G. lucidum* extract or 10 μg/mL ganoderic acid A, and induced to differentiate by adding 1.5 mM $CaCl_2$ under 20 μM cortisol. The incubation period was 24 h. CLDN1 (A) and CLDN4 (B) expression in the cells was visualized using immunostaining. Nuclei were counterstained with Hoechst 33342. Scale bar = 40 μm.

Conversely, chronic stress is associated with various health issues, including reduced skin barrier function,[14,15] dryness,[7] and itching.[16] Specifically, the decrease in barrier function is linked to elevated cortisol levels due to chronic stress.[14] Cortisol is primarily secreted from the adrenal cortex through the activation of the HPA axis, but it has also been reported to be produced by epidermal keratinocytes.[17] However, the concentration of cortisol produced within epidermal keratinocytes is lower compared to blood cortisol levels,[10,13] and it is presumed that the impact of cortisol due to chronic stress is more significantly influenced by cortisol secreted from the adrenal cortex. As blood cortisol levels also temporarily increase under normal physiological conditions, it is unclear if these fluctuations accurately reflect the impact of cortisol during chronic stress. Therefore, we hypothesized in this study that persistently high cortisol levels during chronic stress contribute to stress-related skin problems.

When inducing differentiation of epidermal keratinocytes, 20 μM cortisol, a concentration higher than typical blood levels, reduced TEER, an indicator of TJ formation ability. This aligns with reports that cortisol inhibits keratinocyte differentiation,[18] suggesting that elevated cortisol concentrations may suppress barrier function. To elucidate the impact of chronic stress on skin under these conditions, epidermal keratinocytes were subjected to cortisol treatments at varying frequencies, and we assessed their effects on barrier function.

Cells treated temporarily with cortisol before differentiation induction showed minimal or suppressed effects of cortisol on barrier function. Conversely, continuous cortisol treatment before differentiation induction significantly heightened the negative impact of cortisol on barrier function. These results indicated that sustained cortisol exposure is associated with decreased barrier function, consistent with chronic stress effects.

Cortisol metabolic enzymes include 11β-HSD1, which converts inactive cortisone to active cortisol, and 11β-HSD2, which converts cortisol to cortisone. Differences in the expression levels of these enzymes influence the pharmacological activity of glucocorticoids.[19] Both 11β-HSD1 and 11β-HSD2 are expressed in epidermal keratinocytes,[20,21] and their expression levels can be altered via cortisol treatment.[22,23] Thus, variations in cortisol metabolic enzyme expression may contribute to the exacerbation of decreased barrier function caused in a chronic stress model. We investigated how different frequencies of cortisol treatment affect the expression of 11β-HSD1 and 11β-HSD2. Our findings revealed that temporary stress significantly increased 11β-HSD2 mRNA expression, aligning with studies showing that a single dose of the synthetic glucocorticoid dexamethasone enhances 11β-HSD2 mRNA expression in epidermal keratinocytes[22]. In contrast, chronic stress did not increase 11β-HSD2 mRNA expression but significantly increased 11β-HSD1 mRNA expression. This finding aligns with a study showing that continuous administration of corticosterone, a homologue of human cortisol, increases 11β-HSD1 mRNA expression in mice.[23] In the HPA axis, cortisol secretion is strictly regulated by a negative feedback mechanism. When blood cortisol levels rise, the secretion of corticotropin-releasing hormone and adrenocorticotropic hormone from the hypothalamus and pituitary gland is suppressed. This feedback mechanism prevents excessive cortisol secretion and maintains homeostasis. Conversely, it has been reported that chronic stress, such as depression, leads to the disruption of the negative feedback mechanism.[24] The increase in 11β-HSD2 mRNA expression under temporary stress is thought to be a change that reduces intracellular cortisol levels, similar to the negative feedback mechanism of the HPA axis. In contrast, under chronic stress, 11β-HSD2 mRNA expression does not increase, while 11β-HSD1 mRNA expression increases. This phenomenon is considered analogous to the disruption of the negative feedback mechanism caused by chronic stress. It is suggested that epidermal keratinocytes may regulate the effects of cortisol by altering the expression levels of cortisol metabolic enzymes. Thus, under chronic stress conditions, the increased expression of 11β-HSD1 exacerbates the impact of cortisol, leading to a decline in barrier function.

Chronic stress may increase 11β-HSD1 expression, thus sustaining the effects of cortisol. To address this, we sought an extract that inhibits the conversion of cortisone to cortisol in cells after cortisone is added. Given that cortisone and cortisol readily pass through cell membranes, we measured cortisol levels in the culture supernatant and found that *G. lucidum* extract effectively reduced cortisol levels. We have confirmed the tendency of *G. lucidum* extract to inhibit the expression of 11β-HSD1 mRNA and promote the expression of 11β-HSD2 mRNA (data not shown). This suggests that the cortisol-reducing effect of *G. lucidum* extract is related to changes in the expression levels of 11β-HSD1 and 11β-HSD2.

It has been reported that the fruiting bodies of reishi mushrooms contain triterpenoids, including ganoderic acid A.[25] In the *G. lucidum* extract used for the experiment, we confirmed that it contains approximately 0.18% ganoderic acid A and about 5% total triterpenes (data not shown). We evaluated the effect of *G. lucidum* extract alongside its component ganoderic acid A on the barrier function of CSCs exposed to cortisol. The decrease in TEER was improved, and TJ-related protein expression increased. These findings suggested that *G. lucidum* extract counteracts cortisol-induced barrier function reduction under chronic stress. Additionally, ganoderic acid A may contribute to this protective effect.

These results advance our understanding of the mechanism through which chronic stress contributes to rough skin. It has been reported that atopic dermatitis symptoms exacerbate due to chronic stress, though the detailed mechanisms remain unclear.[26] One potential contributing factor may be the reduction in barrier function caused by chronic stress in individuals with atopic dermatitis symptoms. Additionally, it is suggested that *G. lucidum*, effective for treating chronic stress such as nervous exhaustion and insomnia, may help address rough skin and exacerbation of atopic dermatitis symptoms caused by chronic stress.

5. Conclusion

To elucidate the cause of stress-induced rough skin, we investigated the effects of temporary *versus* chronic stress on epidermal keratinocytes. Our findings indicated that chronic stress increases 11β-HSD1 expression, maintaining elevated cortisol levels and potentially impairing barrier function. Additionally, *G. lucidum* extract reduces cortisol levels and ameliorates the decline in barrier function observed in a chronic stress model, suggesting its potential as a beneficial agent for improving rough skin caused by chronic stress. Further research into the mechanism by which *G. lucidum*

extract improves rough skin under chronic stress is anticipated to provide a more comprehensive understanding of the impact of mental stress on skin health.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations: 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; CLDN-1, claudin-1; CSCs, chronically stressed cells; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; HC, hydrocortisone; HPA axis, hypothalamus–anterior pituitary–adrenal cortex axis; KBM, keratinocyte basal medium; KGM, keratinocyte glowth medium; KGM-HC, KGM without HC; mRNA, messenger RNA; NHEK, normal human neonatal epidermal keratinocyte; NSCs, non-stressed cells; PBS, phosphate-buffered saline; PBS-T, PBS containing 0.05% Tween-20; RT-PCR, reverse transcription PCR; SE, standard error; TEER, transepithelial electrical resistance; TJs, tight junctions; TSCs, temporarily stressed cells

References

1) Y. Tanaka, S. Wakida, Nippon Yakurigaku Zasshi, 137, 185–188 (2011)
2) M. Lawes, C. Hetschko, R. Schöb, G. Stephan, M. Eid, Sci. Rep., 12, 1–10 (2022)
3) L.E. Bautista, P. K. Bajwa, M.M. Shafer, K.M.C. Malecki, C.A. McWilliams, A. Palloni, Int. J. Cardiol. Hypertens., 2, 100012 (2019)
4) V. Vicennati, F. Pasqui, C. Cavazza, U. Pagotto, R. Pasquali, Obesity (Silver Spring), 17, 1678–1683 (2009)
5) N.A. Duggal, J. Upton, A.C. Phillips, P. Hampson, J. M. Lord, Age (Omaha), 37, 9748 (2015)
6) H. Zhang, M. Wang, X. Zhao, Y. Wang, X. Chen, J. Su, Brain Behav. Immun., 116, 286–302 (2024)
7) E. Choi, B.E. Brown, D. Crumrine, S. Chang, M. Man, P.M. Elias, K.R. Feingold, J. Invest. Dermatol., 124, 587–595 (2005)
8) L. Wang, J.Q. Li, J. Zhang, Z.M. Li, H.G. Liu, Y.Z. Wang, RSC Adv., 69, 42084–42097 (2020)
9) H. Nakamura, Shokuhin to Kaihatsu, 23, 62–65 (1988)
10) C. Skobowiat, R.M. Sayre, J.C. Dowdy, A.T. Slominski, Br. J. Dermatol., 168, 595–601 (2013)
11) S. Matsumura, M. Terao, S. Itami, I. Katayama, Dermatoendocrinol, 9, e1412018 (2017)
12) C.J. Merz, O. T. Wolf, Neurosci. Biobehav. Rev., 142, 104901 (2022)
13) C. Jones, C. Gwenin, Physiol. Rep., 24, e14644 (2021)
14) M. Fukada, E. Kano, M. Miyoshi, R. Komaki, T. Watanabe, Chem. Senses, 37, 347–356 (2012)
15) N.Y. Schürer, C. Symanzik, O. Kukshausen, R. Stürmer, Skin Res. Technol., 6, e13745 (2024)
16) R.S. Golpanian, H. S. Kim, G. Yosipovitch, Clin. Ther., 42, 745–756 (2020)
17) A. Slominski, B. Zbytek, G. Nikolakis, P.R. Manna, C. Skobowiat, M. Zmijewski, W. Li, Z. Janjetovic, A. Postlethwaite, C.C. Zouboulis, R. C. Tuckey, J. Steroid Biochem. Mol. Biol., 137, 107–123 (2013)
18) H. Lee, E.J. Choi, E.J. Kim, E.D. Son, H.J. Kim, W.S. Park, Y.G. Kang, K.O. Shin, K. Park, J.C. Kim, S.N. Kim, E. H. Choi, Sci. Rep., 11, 11920 (2021)
19) L. Jiang, M. Zhou, J. Deng, Y. Sun, K. Zuo, R. Zheng, J. Shi, Y. Lai, Eur. Arch. Otorhinolaryngol., 276, 131–137 (2019)
20) N. Cirillo, S. S. Prime, J. Cell. Biochem., 112, 1499–1505 (2011)
21) M. Fukaya, Indian J. Dermatol., 62, 440 (2017)
22) O. Stojadinovic, B. Lee, C. Vouthounis, S. Vukelic, I. Pastar, M. Blumenberg, H. Brem, M. T. Canic, J. Biol. Chem., 282, 4021–4034 (2007)
23) A. Tiganescu, M. Hupe, Y. Uchida, T. Mauro, P. M. Elias, W.M. Holleran, Endocrinology, 159, 547–556 (2018)
24) E. Fitzgerald, Clinical Depression, 9, 4 (2023)
25) H. Zhang, H. Jiang, X. Zhang, S. Tong, J. Yan, J. Anal. Methods Chem., 2018, 1675721 (2018)
26) L. Lönndahl, S. Abdelhadi, M. Holst, S. Lonne-Rahm, K. Nordlin, B. Johansson, A. Dermatol., 35, 342–347 (2023)