Original Article

Gallic Acid Alleviates Psoriasis Keratinization and Inflammation by Regulating BRD4 Expression

(psoriasis / gallic acid / BRD4 / keratinocytes / hyperproliferation / inflammation)

LI ZHANG[1], QIAOYUAN YE[2], SAIYANG GAN[1], HUAN LIU[1], QING ZHANG[1], SHUANGSHUANG WANG[1], CAN CHENG[3]

[1]Dermatology Department, ShenZhen Qianhai Shekou Free Trade Zone Hospital, China
[2]Department of Dermatology and Venereology, Second Clinical Medical College of Guangdong Medical University, China
[3]Shenzhen Polytechnic, China

Abstract. Psoriasis is a chronic non-contagious autoimmune disease. Gallic acid is a natural compound with potential health benefits, including antioxidant, anticancer, antiviral and antibacterial properties. Nevertheless, the influence of gallic acid on psoriasis has not been fully determined. This investigation aimed to discover the effect of gallic acid on psoriasis. Thirty-one pairs of psoriatic skin tissues and healthy adult human skin tissues were collected. Human keratinocytes (HaCaT cells) were transfected with interleukin 17A (IL-17A) to create the psoriatic keratinocyte model. The content of bromodomain-containing protein 4 (BRD4) microRNA was assessed using qRT-PCR testing. The content of BRD4 was detected by Western blotting. Cell migration was evaluated by conducting a wound healing assay. Cell proliferation was determined using an EdU assay. Apoptosis was detected by the TUNEL assay. The contents of interferon gamma (IFN-γ), IL-6, IL-8 and IL-17 were detected by ELISA. BRD4 was up-regulated in psoriatic skin tissues and in the IL-17A group compared to the healthy adult human skin tissues and the control group. Silencing BRD4 inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells. Conversely, BRD4 over-expression promoted cell migration, proliferation and inflammatory response but suppressed apoptosis in IL-17A-treated HaCaT cells. Gallic acid repressed cell migration, proliferation and inflammatory response but induced apoptosis in HaCaT cells transfected with IL-17A by down-regulating BRD4. Gallic acid represses cell migration, proliferation and inflammatory response but induces apoptosis in IL-17A-transfected HaCaT cells by down-regulating BRD4.

Received November 28, 2023. Accepted January 11, 2024.

Corresponding author: Can Cheng, Shenzhen Vocational and Technical College, No.13 Tongfa Road, Xili, Nanshan District, Shenzhen, China; e-mail: ccan1256@163.com

Abbreviations: BRD4 – bromodomain-containing protein 4, DAPI – 4',6-diamidino-2-phenylindole, ELISA – enzyme-linked immunosorbent assay, GAPDH – glyceraldehyde-3-phosphate dehydrogenase, HaCaT cells – human keratinocytes, IFN-γ – interferon gamma, IL – interleukin.

Introduction

Psoriasis is an autoimmune disease characterized by hyperproliferation and inflammatory reactions of keratinocytes (Griffiths at al., 2021). It is typically identified by erythematous, scaly patches of skin, often found on the scalp, knees, elbows, palms and soles of the feet, but it can also affect other parts of the body (Kamiya et al., 2019). Research suggests that psoriasis may be associated with T cells, inflammatory cytokines and immune dysregulation (Petit et al., 2021). Patients should closely monitor changes in their condition, follow their healthcare provider's advice and adopt a healthy lifestyle, including maintaining a proper weight, managing stress and triggers, and keeping their skin clean and moisturized (Rendon and Schäkel, 2019). Psoriasis is caused by the abnormal function of keratinocytes, the primary cells of the epidermis. Under normal conditions, keratinocytes are the main constituents of the epidermis and undergo a regular life cycle. The keratinocytes migrate from the basal layer to the horny layer within the epidermis. However, in psoriasis, the keratinocytes' life cycle is accelerated, leading to their excessive proliferation and shedding, resulting in red patches and scales (Benhadou et al., 2019; Zhou et al., 2022). Therefore, discovering drugs that can effectively inhibit hyperproliferation and inflammation of keratinocytes is imperative to the management of psoriasis.

Gallic acid is a naturally occurring organic acid found widely in various fruits and vegetables, particularly in berries such as strawberries, raspberries and pomegran-

ates. It has been extensively studied and gained significant attention due to its potential health benefits (Bai et al., 2021). Gallic acid possesses powerful antioxidant properties capable of neutralizing free radicals in the body and reducing oxidative stress on cells (Pereira et al., 2018; de Melo et al., 2022). This plays a vital role in preventing heart disease, cancer and inflammation (Yan et al., 2019; Sohrabi et al., 2020; Bai et al., 2021; Jiang et al., 2022). Gallic acid can impede the expansion of cancer cells and stimulate apoptosis, thereby exhibiting potential benefits for cancer prevention and treatment (Jiang et al., 2022). Further, gallic acid exhibits an antiviral effect, boosting immune system function and defending against infections (da Silva, 2021; He et al., 2022). Moreover, Fan et al. (2019) and Wang et al. (2018) established that gallic acid has anti-allergic properties, alleviating allergy symptoms, such as allergic rhinitis and asthma, and inflammatory responses by modulating the levels of inflammatory-related factors. Therefore, we speculate that gallic acid may regulate the immune system and, thus, the progression of psoriasis.

Bromodomain-containing protein 4 (BRD4) is a protein that plays a significant regulatory role within the cell nucleus (Liang et al., 2021). BRD4 possesses two main domains: N-terminal and C-terminal. These domains enable BRD4 to interact with chromatin and participate in the regulation of gene transcription (Donati et al., 2018). In recent years, BRD4 has garnered considerable attention in cancer research. It has been connected to the progression of various cancers, including breast cancer, prostate cancer, lung cancer and haematological malignancies (Donati et al., 2018; Jin et al., 2018; Wu et al., 2020; Gao et al., 2021; Wang et al., 2022). Sun and Yang (2021) found that down-regulation of BRD4 repressed growth and stimulated apoptosis of psoriatic keratinocytes. Consequently, we suggest that BRD4 may be a possible target for treating psoriasis.

In this study, psoriatic skin tissues were collected and HaCaT cells were transfected with interleukin-17A (IL-17A) to create the psoriatic keratinocyte model. Knockdown and over-expression vectors of BRD4 were synthesised to confirm the influence of BRD4 on psoriasis. We also examined the influence of gallic acid on IL-17A-induced keratinocytes and its regulatory impact on BRD4. This study will provide a new therapeutic idea and gene target for the management of psoriasis.

Material and Methods

Human subjects

The psoriatic skin tissues (N = 31) were obtained from human subjects with psoriasis who had undergone cosmetic surgery. Healthy adult human skin tissues (N = 31) were taken from healthy subjects who had undergone cosmetic surgery. All subjects signed the informed consent. The research was approved by the Ethical Committee of the hospital.

Cell culture

For this study, human keratinocytes (HaCaT cells) were purchased from the JCRB cell bank (Ibaraki, Japan). The HaCaT cells were maintained in Dulbecco's Modified Eagle's Medium (Sigma-Aldrich, St. Louis, MO) supplemented with 10 % foetal bovine serum (Sigma) and maintained in 5 % CO_2 at 37 °C. To build a psoriasis-like keratinocyte model, the HaCaT cells were transfected with IL-17A (25 nanograms per millilitre, Sigma) for 24 hours and named the IL-17A group (Tu et al., 2020). Control cells were treated with the same volume of phosphate-buffered saline (Sigma). For gallic acid treatment, HaCaT cells were exposed to 0, 10, 20 and 40 μM of gallic acid (Sigma) for 48 hours before IL-17A treatment.

Cell transfection

Small interfering RNA against BRD4 (si-BRD4) and the control (si-NC) were manufactured by Sangon Biotech (Shanghai, China). BRD4 complementary DNA was inserted into the pcDNA3.0 vector (pcDNA-BRD4) and transfected into HaCaT cells to modulate the level of BRD4. As a control, transfection was adopted using pcDNA3.0 with a control sequence (pcDNA-NC). All sequences were synthesised by Sangon Biotech. Lipofectamine 2000 (Invitrogen, Carlsbad, CA) was used for transfection following the manufacturer's instructions. After 48 hours, the subsequent tests were performed.

qRT-PCR

RNA was extracted using TRIzol® (Invitrogen) in compliance with the accompanying instructions. Reverse transcription was carried out using the PrimeScript™ RT Reagent kit (TaKaRa, Tokyo, Japanese). SYBR® Green Supermix (TaKaRa) was then used to examine BRD4 expression levels. The primers are displayed in Table 1. Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) was used as a reference gene. The comparative gene microRNA level was assessed using the $2^{-\Delta\Delta Cq}$ method.

Western blot

Tissues and cells were treated with lysis buffer (Invitrogen). Next, the protein levels were quantified using the bicinchoninic acid protein assay kit (Sigma). The proteins were detached by sodium dodecyl sulphate-polyacrylamide gel electrophoresis and moved to poly-

Table 1. Primers for qRT-PCR

Name		Primers for PCR (5'-3')
BRD4	Forward	CTAGCGTCTCAGAGTGCCTG
	Reverse	TGCCTCTTGGGCTTGTTAGG
GAPDH	Forward	CAAATTCCATGGCACCGTCA
	Reverse	GACTCCACGACGTACTCAGC

vinylidene difluoride membranes (Invitrogen). After blocking, the membranes were exposed to primary antibodies against BRD4 (ab128874; 1 : 1000; Abcam, Cambridge, MA) and GAPDH (ab8245; 1 : 1000; Abcam) overnight at 4 °C. The membranes were then exposed to goat anti-rabbit immunoglobulin G (ab205718; 1 : 2500; Abcam) for two hours. The protein signals were ascertained using an enhanced chemiluminescence kit (Sigma). Protein levels were semi-quantified using ImageJ software.

Wound healing assay

The treated HaCaT cells (3×10^5 cells per well) were planted into a 6-well culture plate. The monolayer cells were then scratched using a 20-microlitre pipette tip and starved. The cells continued to be cultivated for 24 hours. The images of the scratch area were taken with a microscope (Leica, Wetzlar, Germany) at 0 hours and 24 hours (100× magnification). The relative wound widths were evaluated using ImageJ.

EdU staining

The proliferation of HaCaT cells was assessed using an EdU assay kit (Sigma) in compliance with its specifications. The treated HaCaT cells (5×10^4 cells per well) were then seeded into a 24-well culture plate and cultivated for 24 hours. After that, 4',6-diamidino-2-phenylindole (DAPI) and merge stains were supplemented. Finally, proliferation images were observed under a fluorescence microscope (200× magnification; Leica).

TUNEL staining

Apoptosis was investigated by applying a TUNEL assay kit (Invitrogen). The HaCaT cells were treated with paraformaldehyde (4 %; Sigma) for one hour and then exposed to Triton X-100 (0.1 %; Sigma) for five minutes. Thereafter, the HaCaT cells were treated with the TUNEL reagent (Invitrogen) for one hour. Next, 50 microlitres of 3,3'-diaminobenzidine (DAB; Invitrogen) was applied for 10 minutes in compliance with the instructions. Finally, the HaCaT cells were exposed to DAPI (Invitrogen) for 10 minutes. The cell images were observed through a fluorescence microscope (200× magnification; Leica) and evaluated using ImageJ software.

Enzyme-linked immunosorbent assay

An enzyme-linked immunosorbent assay (ELISA) was performed to evaluate the secretion of inflammatory cytokines interferon gamma (IFN-γ), IL-6, IL-8 and IL-17. The cell supernatants were collected and analysed using IFN-γ (ab174443; Abcam), IL-6 (ab178013; Abcam), IL-8 (ab214030; Abcam) and IL-17 ELISA kits (ab119535; Abcam), following the kits' instructions.

Statistical assay

All tests were completed in triplicate. Statistics were exhibited as mean ± SD. GraphPad Prism 8.0 software was used for statistical analysis. Differences were evaluated by Student's *t*-test or analysis of variance. $P < 0.05$ was considered statistically significant.

Results

BRD4 was up-regulated in psoriasis

First, we examined the level of BRD4 expression in psoriasis. We found that the BRD4 expression was greater in the psoriatic skin tissues compared to the healthy adult human skin tissues (Fig. 1A–B). HaCaT cells were transfected with IL-17A to create the psoriatic keratinocyte model. We also observed that BRD4 expression was higher in the IL-17A group than in the control cells (Fig. 1C). These results show that BRD4 is up-regulated in psoriasis.

Silencing BRD4 inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells

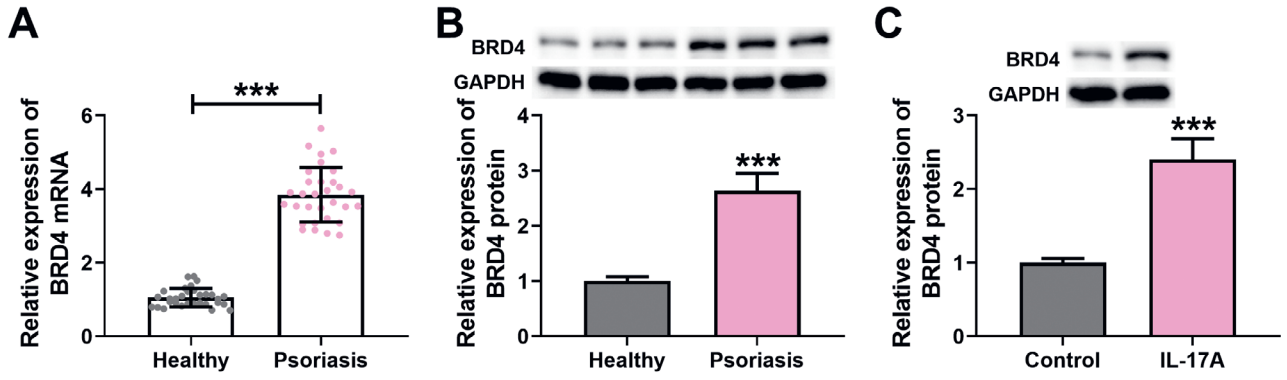

Fig. 1. BRD4 was up-regulated in psoriasis. (**A**) The content of BRD4 mRNA was determined using qRT-PCR. (**B**) The content of BRD4 in skin tissues was determined by Western blot. (**C**) The content of BRD4 in HaCaT cells (treated with IL-17A or control) was determined by Western blot. $^{***}P < 0.001$.

We found that the expression of BRD4 was diminished by si-BRD4 transfection in IL-17A-treated HaCaT cells (Fig. 2A). Additionally, we observed that cell migration (Fig. 2B) and proliferation (Fig. 2C) were reduced, but apoptosis (Fig. 2D) was increased by si-BRD4 transfection in IL-17A-treated HaCaT cells. Moreover, the levels of inflammatory factors (IFN-γ, IL-6, IL-8 and IL-17) noticeably declined by BRD4 knockdown in IL-17A-stimulated HaCaT cells (Fig. 2E–H). Thus, we confirmed that silencing BRD4 inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells.

BRD4 over-expression promoted cell migration, proliferation and inflammatory response but suppressed apoptosis in IL-17A-treated HaCaT cells

We explored the effect of BRD4 over-expression on IL-17A-treated HaCaT cells and found that the level of BRD4 expression was increased by pcDNA-BRD4 transfection in IL-17A-treated HaCaT cells (Fig. 3A). In addition, we found that the IL-17A-treated HaCaT cells' migration (Fig. 3B), proliferation (Fig. 3C) and inflammatory factor (IFN-γ, IL-6, IL-8 and IL-17) levels (Fig. 3E–H) were increased, but apoptosis (Fig. 3D) was reduced by BRD4 up-regulation in the pcDNA-NC group. Therefore, we suggest that BRD4 over-expression promotes cell migration, proliferation and inflammatory response but suppresses apoptosis in IL-17A-treated HaCaT cells.

Gallic acid inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells

We analysed the influence of gallic acid on IL-17A-treated HaCaT cells. The results revealed that, compared to the 0 μM of gallic acid group, cell migration (Fig. 4A), cell proliferation (Fig. 4B) and inflammatory factor (IFN-γ, IL-6, IL-8 and IL-17) levels (Fig. 4D–G) were inhibited with increasing doses of gallic acid in IL-17A-treated HaCaT cells. However, the IL-17A-treated HaCaT cells' apoptosis (Fig. 4C) was increased with the gallic acid dose. We found that various functions of the cells were significantly altered when treated

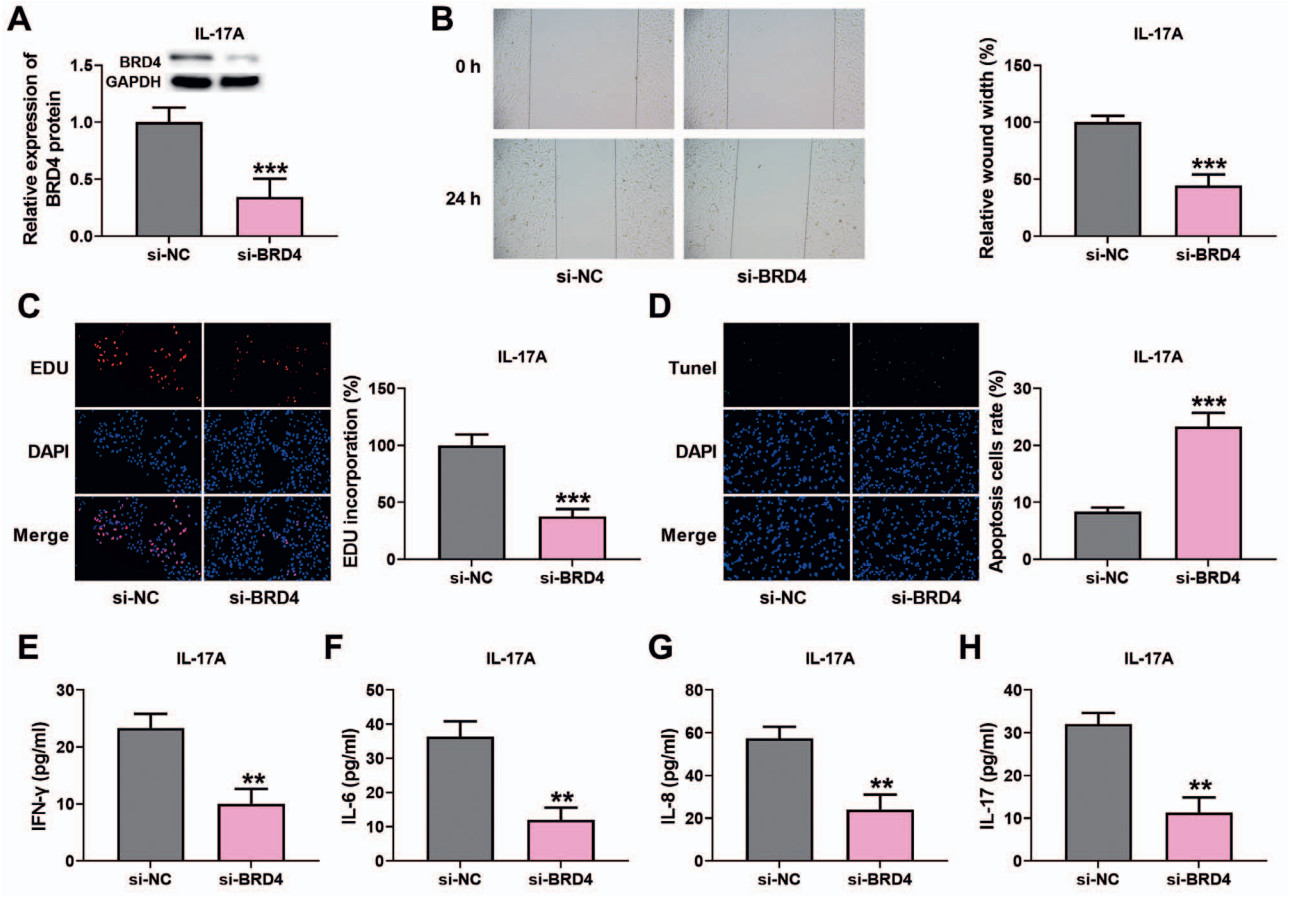

Fig. 2. Knockdown of BRD4 inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells. (**A**) The content of BRD4 was determined by Western blot. (**B**) Cell migration was determined by the wound healing assay. (**C**) Cell proliferation was determined by the EdU assay. (**D**) Apoptosis was determined by the TUNEL assay. (**E–H**) The levels of IFN-γ, IL-6, IL-8 and IL-17 were determined by ELISA. $^{**}P < 0.01$, $^{***}P < 0.001$.

with 20 μM of gallic acid, so we chose the 20-μM gallic acid group for further study in the follow-up experiment. Taken together, these results confirmed that gallic acid inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells.

Gallic acid modulated IL-17A-induced HaCaT cells by down-regulating BRD4

We performed restoration tests and observed that the level of BRD4 was reduced after gallic acid treatment in IL-17A-treated HaCaT cells, while this influence declined by BRD4 up-regulation (Fig. 5A). This result indicates that gallic acid can reduce the level of BRD4. Moreover, gallic acid could obviously impede cell migration (Fig. 5B), proliferation (Fig. 5C) and inflammatory factor (IFN-γ, IL-6, IL-8 and IL-17) levels (Fig. 5E–H) but increased apoptosis (Fig. 5D) in IL-17A-treated HaCaT cells. In contrast, the BRD4 up-regulation reversed these effects (Fig. 5B–H). These outcomes confirmed that gallic acid inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-induced HaCaT cells by down-regulating BRD4.

Discussion

In this study, we established that BRD4 was up-regulated in the psoriatic skin tissues and in the IL-17A group compared to the healthy adult human skin tissues and the control group. In addition, we observed that silencing BRD4 expression inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells. Conversely, BRD4 up-regulation promoted cell migration, proliferation and inflammatory response but suppressed apoptosis in IL-17A-treated HaCaT cells. Finally, we also found that gallic acid inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells by down-regulating BRD4. In conclusion, gallic acid repressed cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells by down-regulating BRD4.

There are many clinical symptoms in patients with psoriasis, which greatly affects their quality of life (Arm-

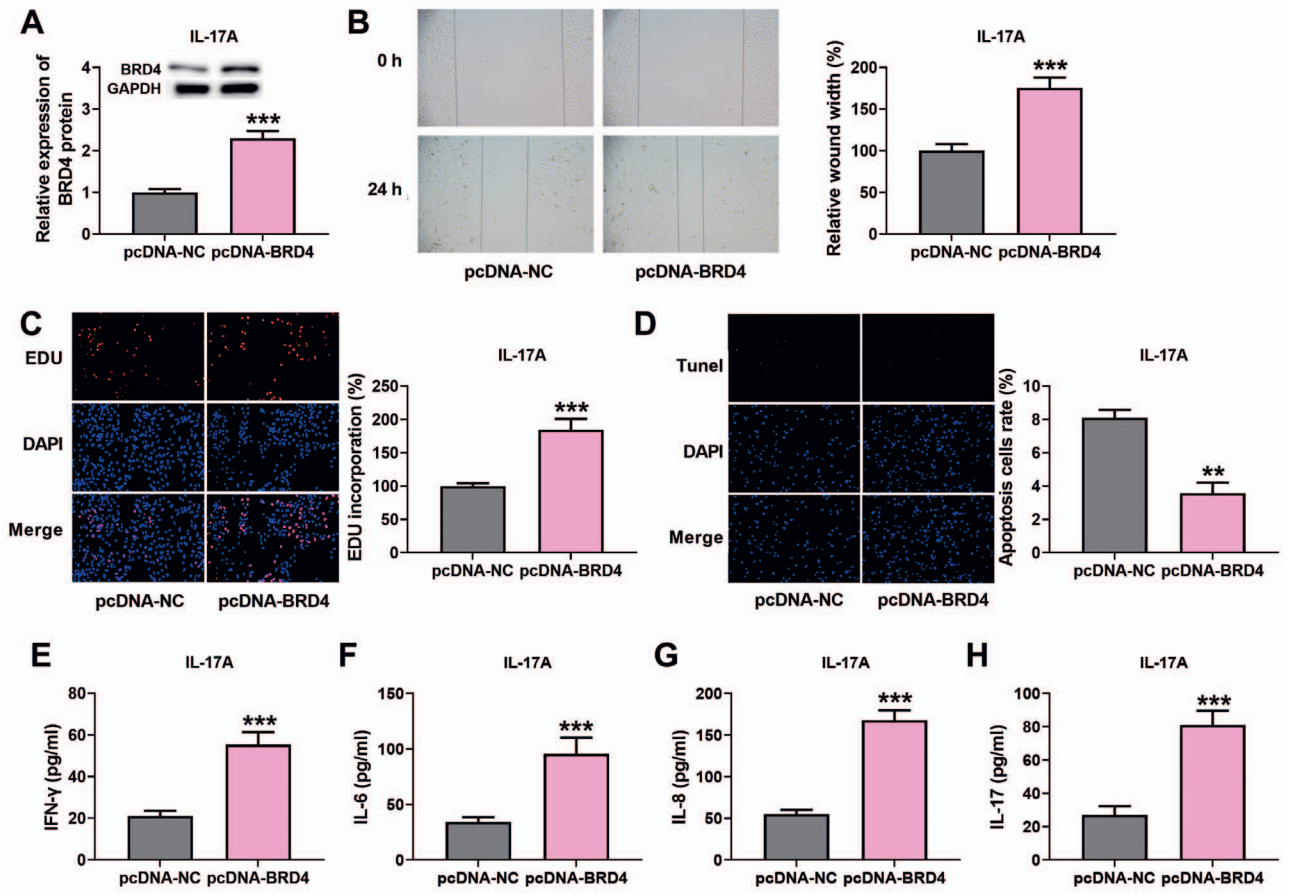

Fig. 3. BRD4 over-expression promoted cell migration, proliferation and inflammatory response but suppressed apoptosis in IL-17A-treated HaCaT cells. (**A**) The content of BRD4 was determined by Western blot. (**B**) Cell migration was determined by the wound healing assay. (**C**) Cell proliferation was determined by the EdU assay. (**D**) Apoptosis was determined by the TUNEL assay. (**E–H**) The levels of IFN-γ, IL-6, IL-8 and IL-17 were determined by ELISA. $^{**}P < 0.01$, $^{***}P < 0.001$.

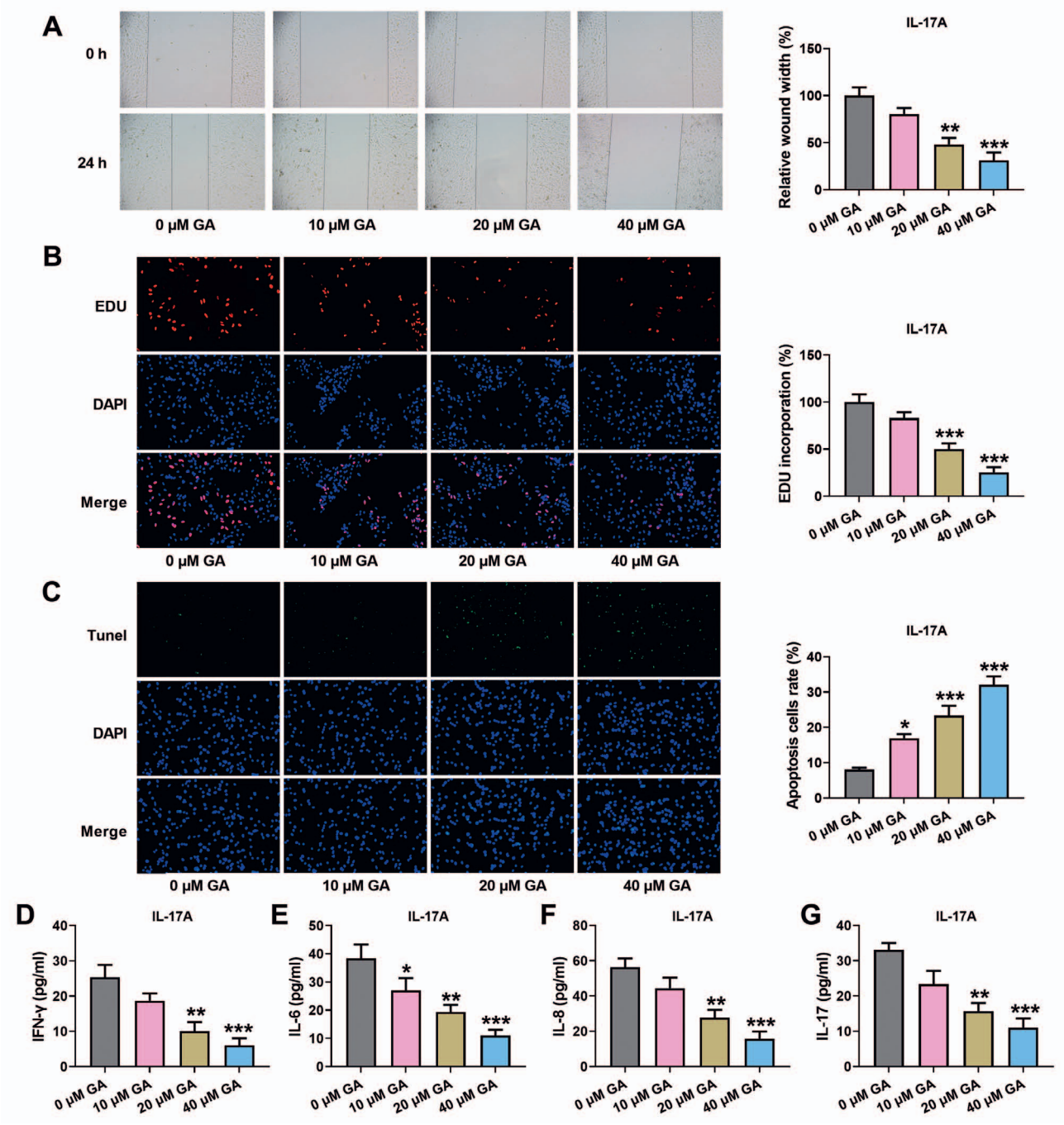

Fig. 4. Gallic acid inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells. (**A**) Cell migration was determined by the wound healing assay. (**B**) Cell proliferation was determined by the EdU assay. (**C**) Apoptosis was determined by the TUNEL assay. (**D–G**) The levels of IFN-γ, IL-6, IL-8 and IL-17 were determined by ELISA. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

strong et al., 2020). Psoriasis is usually diagnosed based on the appearance of skin lesions and medical history; dermatologists may perform clinical examinations and skin biopsies for confirmation (Brandon et al., 2019; Fujita et al., 2022). While psoriasis cannot be cured, its symptoms can be managed, and flare-ups can be reduced. Common treatment options include corticosteroid creams, vitamin D_3 derivatives, keratolytics, using specific wavelengths of ultraviolet light to target affected areas, immunomodulators, small molecule targeted therapies and biologic agent medications that modulate the immune system, administered via intravenous or subcutaneous injections, such as tumour necrosis factor alpha (TNF-α) inhibitors, IL-23 inhibitors and IL-17A inhibitors (Brandon et al., 2019; Rendon and Schäkel, 2019; Bakshi et al., 2020; Tokuyama and Mabuchi, 2020; Kaeley et al., 2021).

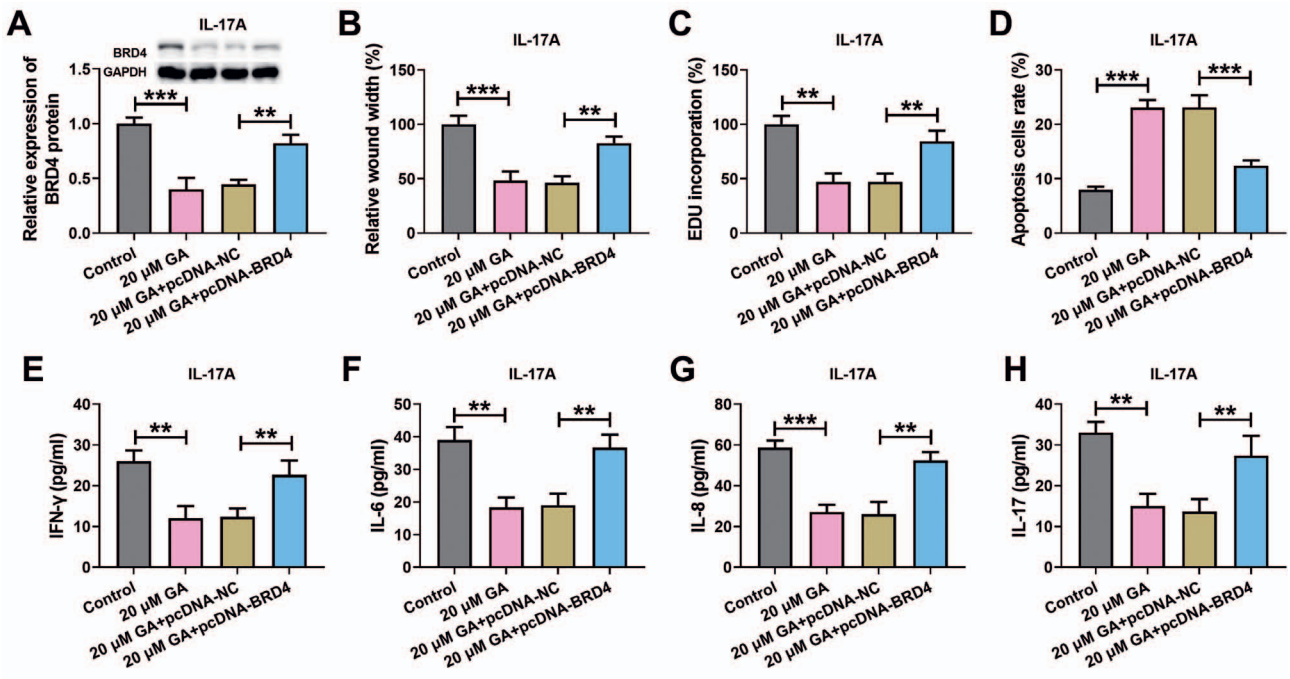

Fig. 5. Gallic acid modulated IL-17A-induced HaCaT cells by down-regulating BRD4. (**A**) The content of BRD4 was determined by Western blot. (**B**) Cell migration was determined by the wound healing assay. (**C**) Cell proliferation was determined by the EdU assay. (**D**) Apoptosis was determined by the TUNEL assay. **(E–H)** The levels of IFN-γ, IL-6, IL-8 and IL-17 were determined by ELISA. $^{**}P < 0.01$, $^{***}P < 0.001$.

In psoriasis patients, abnormal stimulation of the immune system causes excessive proliferation of keratinocytes (Orsmond et al., 2021). Normally, the life cycle of a keratinocyte is around 28 days, but in psoriasis patients, this cycle is shortened to three to four days. This means that the keratinocytes do not have enough time to mature and shed, leading to their accumulation on the skin surface, forming thick scales (Furue et al., 2020). In psoriasis, the excessive proliferation of keratinocytes is accompanied by their abnormal differentiation (Ni and Lai, 2020). Normally, when keratinocytes migrate from the basal layer to the epidermis, they gradually differentiate into mature keratinocytes, forming the skin barrier. However, in cases of psoriasis, this differentiation process is disrupted, and the keratinocytes do not fully mature, leading to hyperkeratosis and scale formation on the surface of the patches (Rioux et al., 2020). Moreover, abnormal stimulation of the immune system is also linked to the pathogenesis of psoriasis (Albanesi et al., 2018). In psoriatic plaques, there is an increased number and activation of T cells and inflammatory cytokines (Hu et al., 2021). These inflammatory responses further stimulate the abnormal proliferation of keratinocytes and release of inflammatory mediators, forming the characteristic psoriatic lesions (Dainichi et al., 2018; Furue et al., 2019; Vičić et al., 2021). To summarize, psoriasis is caused by the abnormal proliferation, differentiation and inflammatory response of keratinocytes (Shou et al., 2021). Recognizing the relationship between psoriasis and keratinocytes helps us to better understand the pathogenesis of the disease and provides insights for developing treatment strategies.

BRD4 plays a critical role within the cell nucleus and participates in the regulation of gene transcription (Wang et al., 2021). BRD4 locates to specific regions on chromatin by interacting with acetylated histones. Its bromodomain binds to acetylated lysine residues, recruiting other transcriptional regulatory factors and enzymes involved in transcriptional regulation (Donati et al., 2018). The binding and regulatory activities of BRD4 are closely associated with processes such as transcription initiation, enhancer activity and recruitment of transcription factors (Altendorfer et al., 2022). BRD4 is also associated with the occurrence and development of cancer, making it a potential target for cancer therapy (Donati et al., 2018). Further research on BRD4 will contribute to a deeper understanding of its role in cellular regulation, potentially leading to the development of novel treatment strategies. Pan et al. (2019) reported that the number of HaCaT cells was diminished by the miR-125b-mediated suppression of BRD4 content. Additionally, Lu et al. (2023) found that BRD4 could modulate the proliferation, migration and inflammation of IL-22-induced keratinocytes. In this study, we detected that BRD4 was up-regulated in the psoriatic skin tissues and in the IL-17A group compared to the healthy adult human skin tissues and the control group. Moreover, we observed that BRD4 silencing inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells. Con-

versely, BRD4 up-regulation promoted cell migration, proliferation and inflammatory response but suppressed apoptosis in IL-17A-treated HaCaT cells. These results correspond with the reports of Sun and Yang (2021) and Lu et al. (2023). We also found that gallic acid could reduce the level of BRD4 in IL-17A-treated HaCaT cells, suggesting that gallic acid may affect the progression of psoriasis by regulating BRD4.

Gallic acid is a natural compound with potential health benefits, including antioxidant, anticancer, antiviral and antibacterial properties (Bai et al., 2021). Research has also revealed the cardiovascular health benefits of gallic acid, including its ability to lower cholesterol levels, thus reducing the risk of atherosclerosis (Al Zahrani et al., 2020). It helps protect the liver from damage and provides certain protective effects against metabolic diseases such as diabetes and obesity (Xu et al., 2021). However, further scientific research is needed to determine its specific therapeutic effects and applications to psoriasis. Tsiogkas et al. (2023) reported that gallic acid could lower the levels of IFN-γ and IL-17 in patients with psoriasis. Further, Sheikh et al. (2023) confirmed that gallic acid may have a possible use for treating inflammatory diseases such as psoriasis. Moreover, Zhang et al. (2018) found that gallic acid could reduce the over-expression of keratin 17 in psoriasis. Our experiments revealed that gallic acid inhibited cell migration, proliferation and inflammatory response but induced apoptosis in IL-17A-treated HaCaT cells by down-regulating BRD4. These results are consistent with the reports of Tsiogkas et al. (2023) and Zhang et al. (2018). However, this study still leaves room for further research. We only verified the effect of gallic acid in a cell model; in a follow-up study, we will investigate it further in an *in vivo* model.

Conclusion

In summary, gallic acid inhibited the proliferation and inflammatory response of IL-17A-treated HaCaT cells by down-regulating BRD4. This study provides a potential effective therapeutic drug for the management of psoriasis and delivers a theoretic basis for new drugs. In addition, we expanded the study of the pathogenesis of psoriasis.

Acknowledgements

Authors sincerely thank Qianhaishekou Free Trade Zone Hospital, Nanshan District, Shenzhen for supporting this study.

Conflicts of interest

All authors declared that they have no conflicts of interest.

References

Al Zahrani, N. A., El-Shishtawy, R. M., Asiri, A. M. (2020) Recent developments of gallic acid derivatives and their hybrids in medicinal chemistry: a review. *Eur. J. Med. Chem*. **204**, 112609.

Albanesi, C., Madonna, S., Gisondi, P. et al. (2018) The interplay between keratinocytes and immune cells in the pathogenesis of psoriasis. *Front Immunol*. **9**, 1549.

Altendorfer, E., Mochalova, Y., Mayer, A. (2022) BRD4: a general regulator of transcription elongation. *Transcription* **13**, 70-81.

Armstrong, A. W., Read, C. (2020) Pathophysiology, clinical presentation, and treatment of psoriasis: a review. *JAMA* **323**,1945-1960.

Bai, J., Zhang, Y., Tang, C. et al. (2021) Gallic acid: pharmacological activities and molecular mechanisms involved in inflammation-related diseases. *Biomed. Pharmacother*. **133**, 110985.

Bakshi, H., Nagpal, M., Singh, M. et al. (2020) Treatment of psoriasis: a comprehensive review of entire therapies. *Curr. Drug Saf*. **15**, 82-104.

Benhadou, F., Mintoff, D., Del Marmol, V. (2019) Psoriasis: keratinocytes or immune cells – which is the trigger? *Dermatology* **235**, 91-100.

Brandon, A., Mufti, A., Sibbald, R. G. (2019) Diagnosis and management of cutaneous psoriasis: a review. *Adv. Skin Wound Care* **32**, 58-69.

da Silva, A. P. G. (2021) Fighting coronaviruses with natural polyphenols. *Biocatal. Agric. Biotechnol*. **37**, 102179.

Dainichi, T., Kitoh, A., Otsuka, A. et al. (2018) The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis. *Nat. Immunol*. **19**, 1286-1298.

de Melo, K. D. C. M., dos Santos Lisboa, L., Queiroz, M. F. et al. (2022) Antioxidant activity of fucoidan modified with gallic acid using the redox method. *Mar. Drugs* **20**, 490.

Donati, B., Lorenzini, E., Ciarrocchi, A. et al. (2018) BRD4 and cancer: going beyond transcriptional regulation. *Mol. Cancer* **17**, 164.

Fan, Y., Piao, C. H., Hyeon, E. et al. (2019) Gallic acid alleviates nasal inflammation via activation of Th1 and inhibition of Th2 and Th17 in a mouse model of allergic rhinitis. *Int. Immunopharmacol*. **70**, 512-519.

Fujita, H., Gooderham, M., Romiti, R. (2022) Diagnosis of generalized pustular psoriasis. *Am. J. Clin. Dermatol*. **23**, 31-38.

Furue, K., Ito, T., Tsuji, G. et al. (2019) Psoriasis and the TNF/IL23/IL17 axis. *G. Ital. Dermatol. Venereol*. **154**, 418-424.

Furue, M., Furue, K., Tsuji, G. et al. (2020) Interleukin-17A and keratinocytes in psoriasis. *Int. J. Mol. Sci*. **21**, 1275.

Gao, R. L., Zeng, C. W., Li, Y. Q. (2021) Research advances in the mechanisms of BRD4 and its inhibitors in hematologic malignancies – Review. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* **29**, 1365-1368.

Griffiths, C. E. M., Armstrong, A. W., Gudjonsson, J. E. et al. (2021) Psoriasis. *Lancet* **397**, 1301-1315.

He, Z., Ma, Y., Chen, X. et al. (2022) Protective effects of intestinal gallic acid in neonatal dairy calves against extended-spectrum beta-lactamase producing enteroaggregative Escherichia coli infection: modulating intestinal homeostasis and colitis. *Front. Nutr*. **9**, 864080.

Hu, P., Wang, M., Gao, H. et al. (2021) The role of helper T cells in psoriasis. *Front. Immunol*. **12**, 788940.

Jiang, Y., Pei, J., Zheng, Y. et al. (2022) Gallic acid: a potential anti-cancer agent. *Chin. J. Integr. Med*. **28**, 661-671.

Jin, X., Yan, Y., Wang, D. et al. (2018) DUB3 promotes BET inhibitor resistance and cancer progression by deubiquitinating BRD4. *Mol. Cell* **71**, 592-605.e4.

Kaeley, G. S., Eder, L., Aydin, S. Z. et al. (2021) Nail psoriasis: diagnosis, assessment, treatment options, and unmet clinical needs. *J. Rheumatol*. **48**, 1208-1220.

Kamiya, K., Kishimoto, M., Sugai, J. et al. (2019) Risk factors for the development of psoriasis. *Int. J. Mol. Sci*. **20**, 4347.

Liang, Y., Tian, J., Wu, T. (2021) BRD4 in physiology and pathology: "BET" on its partners. *Bioessays* **43**, e2100180.

Lu, J., Wang, Y., Wang, J. et al. (2023) Circ_0082476 targets miR-138-5p to promote proliferation, invasion, migration and inflammation in IL-22-treated human keratinocytes by upregulating BRD4. *Int. Immunopharmacol*. **119**, 110095.

Ni, X., Lai, Y. (2020) Keratinocyte: a trigger or an executor of psoriasis? *J. Leukoc. Biol*. **108**, 485-491.

Orsmond, A., Bereza-Malcolm, L., Lynch, T. (2021) Skin barrier dysregulation in psoriasis. *Int. J. Mol. Sci*. **22**, 10841.

Pan, M., Huang, Y., Zhu, X. et al. (2019) MiR-125b-mediated regulation of cell proliferation through the Jagged-1/Notch signaling pathway by inhibiting BRD4 expression in psoriasis. *Mol. Med. Rep*. **19**, 5227-5236.

Pereira, M. M., de Morais, H., Dos Santos Silva, E. et al. (2018) The antioxidant gallic acid induces anxiolytic-, but not antidepressant-like effect, in streptozotocin-induced diabetes. *Metab. Brain Dis*. **33**, 1573-1584.

Petit, R. G., Cano, A., Ortiz, A. et al. (2021) Psoriasis: from pathogenesis to pharmacological and nano-technological-based therapeutics. *Int. J. Mol. Sci*. **22**, 4983.

Rendon, A., Schäkel, K. (2019) Psoriasis pathogenesis and treatment. *Int. J. Mol. Sci*. **20**, 1475.

Rioux, G., Ridha, Z., Simard, M. et al. (2020) Transcriptome profiling analyses in psoriasis: a dynamic contribution of keratinocytes to the pathogenesis. *Genes (Basel)* **11**, 1155.

Sheikh, A., Hazari, S. A., Molugulu, N. et al. (2023) Hyaluronic acid engineered gallic acid embedded chitosan nanoparticle as an effective delivery system for treatment of psoriasis. *Environ. Res.* **238 (Pt 1)**, 117086.

Shou, S., Yang, L., Yang, Y. et al. (2021) Inhibition of keratinocyte ferroptosis suppresses psoriatic inflammation. *Cell Death Dis*. **12**, 1009.

Sohrabi, F., Dianat, M., Badavi, M. et al. (2020) Does gallic acid improve cardiac function by attenuation of oxidative stress and inflammation in an elastase-induced lung injury? *Iran J. Basic Med. Sci*. **23**, 1130-1138.

Sun, X., Yang, P. (2021) Inhibition of BRD4 inhibits proliferation and promotes apoptosis of psoriatic keratinocytes. *Biomed. Eng. Online* **20**, 107.

Tokuyama, M., Mabuchi, T. (2020) New treatment addressing the pathogenesis of psoriasis. *Int. J. Mol. Sci*. **21**, 7488.

Tsiogkas, S. G., Apostolopoulou, K., Mavropoulos, A. et al. (2023) Gallic acid diminishes pro-inflammatory interferon-γ- and interleukin-17-producing sub-populations in vitro in patients with psoriasis. *Immunol. Res*. **71**, 475-487.

Tu, J., Yin, Z., Guo, J. et al. (2020) Acitretin inhibits IL-17A-induced IL-36 expression in keratinocytes by down-regulating IκBζ. *Int. Immunopharmacol*. **79**, 106045.

Vičić, M., Kaštelan, M., Brajac, I. et al. (2021) Current concepts of psoriasis immunopathogenesis. *Int. J. Mol. Sci*. **22**, 11574.

Wang, J., Xu, Y., Rao, X. et al. (2022) BRD4-IRF1 axis regulates chemoradiotherapy-induced PD-L1 expression and immune evasion in non-small cell lung cancer. *Clin. Transl. Med*. **12**, e718.

Wang, W., Tang, Y. A., Xiao, Q. et al. (2021) Stromal induction of BRD4 phosphorylation results in chromatin remodeling and BET inhibitor resistance in colorectal cancer. *Nat. Commun*. **12**, 4441.

Wang, X., Zhao, H., Ma, C. et al. (2018) Gallic acid attenuates allergic airway inflammation via suppressed interleukin-33 and group 2 innate lymphoid cells in ovalbumin-induced asthma in mice. *Int. Forum Allergy Rhinol*. **8**, 1284-1290.

Wu, S. Y., Lee, C. F., Lai, H. T. et al. (2020) Opposing functions of BRD4 isoforms in breast cancer. *Mol. Cell*. **78**, 1114-1132.

Xu, Y., Tang, G., Zhang, C. et al. (2021) Gallic acid and diabetes mellitus: its association with oxidative stress. *Molecules* **26**, 7115.

Yan, X., Zhang, Y. L., Zhang, L. et al. (2019) Gallic acid suppresses cardiac hypertrophic remodeling and heart failure. *Mol. Nutr. Food Res*. **63**, e1800807.

Zhang, J., Li, X., Wei, J. et al. (2018) Gallic acid inhibits the expression of keratin 16 and keratin 17 through Nrf2 in psoriasis-like skin disease. *Int. Immunopharmacol*. **65**, 84-95.

Zhou, X., Chen, Y., Cui, C. et al. (2022) Advances in the pathogenesis of psoriasis: from keratinocyte perspective. *Cell Death Dis*. **13**, 81.