Article

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Fruit Acid Inhibits UV-Induced Skin Aging via PI3K/Akt and NF-κB Pathway Inhibition

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Backgrounds: Ultraviolet (UV) radiation-induced photoaging is a multifaceted biological process. Fruit acids have shown promise in combating photoaging. This study aims to investigate the mechanisms underlying the protective effects of fruit acids on UV-induced skin photoaging.

Methods: Initially, we induced skin photoaging in rats through UV irradiation. Subsequently, the model group received glycolic acid treatment. The reparative effects of glycolic acid on skin tissue morphology and structure were assessed using Hematoxylin-eosin (HE) staining. The influence of glycolic acid on oxidative stress indicators (Superoxide Dismutase (SOD), Glutathione Peroxidase (GSH-Px), Malondialdehyde (MDA), Catalase (CAT)) and levels of cellular inflammatory factors (Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), IL-1β, Interferon-gamma (IFN-γ)) in photoaged skin was evaluated via Enzyme-Linked Immunosorbent Assay (ELISA). Additionally, alterations in collagen expression and levels of proteins associated with the Phosphoinositide 3-kinase/Protein Kinase B (PI3K/Akt) and Nuclear Factor kappa B (NF-κB) signaling pathways were determined through Western blot analysis.

Results: Compared to the model group, the fruit group exhibited a decrease in the thickness of the skin epidermal keratinization layer, an increase in dermal thickness, and more vigorous cortical secretion. Moreover, compared with the model group, the fruit group showed significant increases in SOD activity, CAT, GSH-Px, Collagen I, Collagen III, Collagen VII, and elastin. Conversely, levels of MDA, IL-6, IL-1β, IFN-γ, and TNF-α were lower in the fruit acid group than in the model group. Additionally, fruit acid treatment inhibited the phosphorylation levels of PI3K, Akt, and p65 induced by UV.

Conclusion: Fruit acid demonstrates the ability to diminish the oxidative stress and inflammatory responses in skin photoaging rat models, thereby facilitating collagen recovery and ameliorating symptoms of skin photoaging. Its potential mechanism may entail the inhibition of the activation of the PI3K/Akt and NF-κB signaling pathways.

Keywords: fruit acid; skin photoaging; oxidative stress; inflammatory factor; collagen

Introduction

The skin serves as the primary barrier for direct contact with the external environment and for resisting external stimuli. It plays a crucial role in perceiving the environment, regulating the stability of the microenvironment, and maintaining overall systemic function [1]. Skin aging is a complex biological process characterized by pigmentation, sagging, and wrinkles, which are prominent clinical features, and within the spectrum of external aging, facial skin aging represents a degenerative biological process that significantly impacts the structure of both the skin and facial tissues [2]. The primary factors contributing to skin aging are aging itself and ultraviolet radiation. Prolonged exposure to ultraviolet radiation damages the structural integrity of the skin tissue, leading to aging known as photoaging—a form of exogenous aging. Presently, even younger individuals exhibit signs of premature aging skin due to environmental exposures, posing a significant threat to their quality of life [3]. Studies indicate that individuals with skin photoaging experience weakened removal of oxygen free radicals and undergo oxidative stress damage, resulting in the accumulation of oxygen free radicals in the body, thus contributing to skin aging and pigmentation formation. Therefore, improving oxidative stress responses in individuals with photoaged skin holds significant importance [4,5]. Currently, intense pulsed light therapy stands as the primary treatment approach for skin photoaging [6].

Studies have confirmed that natural hydroxy acids can effectively treat melasma with high efficacy. However, the impact of hydroxy acids on improving oxidative stress and symptoms of skin aging in skin photoaging remains unclear [7]. The Phosphoinositide 3-kinase/Protein Kinase B (PI3K/Akt) and Nuclear Factor kappa B (NF-κB) signaling pathways are known to play regulatory roles in various aspects of skin physiology, including the epidermal barrier, keratinocyte differentiation, cutaneous tumorigenesis, inflammation, and pigmentation [8].

In this study, we aim to uncover the potential mechanisms behind the protective effects of fruit acid treatment on ultraviolet (UV)-induced photoaged skin. Our focus lies on examining the impact of fruit acid treatment on pivotal signaling pathways, including PI3K/Akt and NF-κB, which are known for their crucial roles in cellular survival and inflammatory responses. Furthermore, we aim to investigate the antioxidant properties of fruit acids and their potential in mitigating oxidative stress triggered by UV radiation. By comprehending these mechanisms, we not only contribute to understanding the scientific rationale behind the efficacy of fruit acids but also advance our knowledge of interventions against skin damage caused by UV exposure.

By conducting a comprehensive examination of these molecular and cellular aspects, our study seeks to achieve a thorough understanding of the protective effects of fruit acid treatment on photoaged skin. This understanding holds the potential to guide the development of targeted skincare strategies aimed at addressing the complexities of UV-induced skin aging.

Materials and Methods

Rat Skin Photoaging Model Construction

Forty healthy male Sprague-Dawley (SD) rats, with a clean grade and aged 3–4 months, weighing 300 $\pm$ 10 g, were procured from Shanghai Nanfang Model Biotechnology Co., Ltd., (Shanghai, China) The rats were individually housed in cages with ad libitum access to drinking water. The backs of the rats were treated with an 8% sodium sulfide alcohol solution to remove hair, followed by cleaning with mild detergent. Five small areas, each measuring 1.5 cm $\times$ 1.5 cm, were delineated and marked for subsequent analysis. Over the course of the first week, the rats were exposed to UV irradiation using a homemade UV lamp for 5 days, with each session lasting 20 min. Subsequently, the duration of UV exposure was increased to 25 min per session in the second week. By the fifth week, the rats were exposed to UV irradiation for 30 min per session, maintained for 14 weeks. Euthanasia of the rats was performed via intraperitoneal injection of pentobarbital sodium (110 mg/kg). Ethical approval for this study was obtained from the Medical Ethics Committee of Beijing Chaoyang Hospital Affiliated with Capital Medical University (Approval No.: 2023-126).

Grouping and Intervention Program

Twenty rats that successfully underwent modeling were randomly allocated into two groups: the fruit acid group and the model group, using the number table method. Additionally, ten healthy rats were selected as the control group. Rats in the control and model groups were topically administered normal saline at the designated areas daily. Rats in the fruit acid group were topically treated with a 5% hydroxy acid solution at the designated areas daily, for a duration of 2 min per session. Each group received continuous treatment for 30 days. Experimental rats were anesthetized via intraperitoneal injection of pentobarbital at a concentration of 2% and a dosage of 2.3 mg/kg. All animal experiments were conducted in accordance with the approved guidelines and protocols set by the PUMCH Animal Ethics Committee.

Preparation of Skin Specimen and Skin Digestive Fluid

The skin on the back of each rat was carefully selected, and any fat and loose connective tissue were meticulously removed by scraping. The epidermis was then separated by applying an epidermal separation solution, while the dermis was preserved. Subsequently, the dermis was compressed into tissue blocks using absorbent paper until no water precipitation was observed. The tissue blocks were then stored in a refrigerator at –4 °C for further analysis.

The back tissue specimen, weighing 5 mg, was carefully cut into pieces and placed into a 5 mL tube with a stopper, ensuring thorough mixing. Subsequently, 2 mL of HCl solution was added to the tube, and the mixture was heated in an oven at a temperature set to 125 °C. After 2 h of hydrolysis, 1 mL of NaOH solution with a pH range of 5–7 was added. Finally, a skin digestive solution was prepared by adding water to achieve a total volume of 5 mL.

Histomorphological Examination

The skin tissues from rats in each group were fixed using a 20% formaldehyde solution. Following standard paraffin embedding procedures, the tissues were sectioned to a thickness of 4 μm. Hematoxylin-eosin staining (HE staining) was performed using G1120 stain from Solarbio, Beijing, China. Subsequently, the stained sections were observed and images were captured under a microscope (CKX53, OLYMPUS, Tokyo, Japan).

Masson's Staining Experiment

The tissue samples were initially fixed in 4% paraformaldehyde, followed by a series of steps including dehydration, clearing, infiltration, sectioning, and ribbon-mounting. Subsequently, staining was carried out using the Masson staining kit (G1340) from Solarbio, Beijing, China. After staining, the samples underwent deparaffinization, dehydration, and clearing processes before being mounted. Finally, the stained sections were observed under a microscope (CKX53, OLYMPUS, Tokyo, Japan).

Western Blot

Collect skin tissue samples and homogenize them in an appropriate buffer. Utilize protein extraction buffer to extract proteins from the homogenized tissue, and consider incorporating proteinase inhibitors and phosphatase inhibitors to prevent protein degradation. Concentrate the extracted proteins using a suitable method and ensure uni-

form total protein amounts in the samples by determining protein concentration. Load protein samples onto a Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE) gel and separate them via electrophoresis according to protein size. Transfer the segregated proteins to a polyvinylidene difluoride (PVDF) membrane, typically employing a semi-dry transfer technique. Block the membrane with protein blocking buffer to prevent nonspecific binding. Incubate the membrane with specific primary antibodies: Collagen I (1:1000 dilution; cat no. ab138492, Abcam, Cambridge, UK), Collagen III (1:1000 dilution; cat no. ab184993, Abcam, Cambridge, UK), Collagen VII (1:1000 dilution; cat no. ab309143, Abcam, Cambridge, UK), elastin (1:1000 dilution; cat no. ab307150, Abcam, Cambridge, UK), PI3K (1:1000 dilution; cat no. ab302958, Abcam, Cambridge, UK), Phosphorylated PI3K (p-PI3K) (1:1000 dilution; cat no. Ab283852, Abcam, Cambridge, UK), Akt (1:1000 dilution; cat no. Ab38449, Abcam, Cambridge, UK), Phosphorylated Akt (p-Akt) (1:1000 dilution; cat no. Ab8805, Abcam, Cambridge, UK), p65 (1:1000 dilution; cat no. Ab32536, Abcam, Cambridge, UK), Phosphorylated p65 (p-p65) (1:1000 dilution; cat no. Ab31624, Abcam, Cambridge, UK), and Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) (1:1000 dilution; cat no. Ab9485, Abcam, Cambridge, UK) to bind the target proteins. Wash the membrane to eliminate unbound primary antibodies. Subsequently, incubate the membrane with secondary antibodies (Horseradish Peroxidase (HRP)-conjugated) (1:2000 dilution; cat no. ZB-2305, ZB-2301, ZSGB-BIO, Beijing, China) specific to the primary antibodies. After washing the membrane to remove unbound secondary antibodies, detect the labeled antibodies using a fluorescence imaging system (ChemiDoc Imaging Systems, Bio-Rad, Hercules, CA, USA) to visualize the expression levels of the target proteins. Quantify the expression levels using imageJ analysis software (version 1.5e, National Institutes of Health, Bethesda, MD, USA).

Enzyme-Linked Immunosorbent Assay (ELISA)

The protein extracted from the back skin was exposed to ultraviolet light. The levels of Superoxide Dismutase (SOD) (A001-3-2), Catalase (CAT) (A007-1-1), Malondialdehyde (MDA) (A003-1-1), Glutathione Peroxidase (GSH-Px) (A005-1-2), Interleukin-6 (IL-6) (H007-1-1), IL-1β (H002-1-1), Interferon-gamma (IFN-γ) (H025-1-2), and Tumor Necrosis Factor-alpha (TNF-α) (H052-1-2) were determined via ELISA. The aforementioned kits were procured from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Specific operational procedures were executed following the manufacturer's instructions. Ultimately, the levels of the aforementioned indicators were assessed using a microplate reader (EnSight, PerkinElmer, Waltham, MA, USA).

Statistic Analysis

Statistical analyses were conducted using SPSS 17.0 software (IBM, Armonk, NY, USA). Data visualization was carried out with GraphPad Prism 8.0.2 software (GraphPad Software Inc, San Diego, CA, USA). Results are expressed as mean $\pm$ standard deviation. One-way analysis of variance (ANOVA) was utilized for comparisons among multiple groups, while *t*-tests were employed for between-group comparisons. Statistical significance was established at a p-value < 0.05.

Results

Treatment with fruit acids inhibited the ultraviolet-induced aging process in rat skin tissues. Over a period of 30 days, the dorsal skin of hairless rats was exposed to UV radiation (150 mJ/cm^2) every other day. It was observed that the dorsal skin of hairless rats exposed to UV radiation exhibited markedly reduced lightness compared to control mouse skin (Fig. 1A). Further confirmation of skin photoaging induction was obtained through HE staining (Fig. 1B). In the fruit acid-treated group, the thickness of the skin's keratinized layer was decreased, while the dermis showed increased thickness, heightened cortical secretion activity, and an increased presence of collagen fibers. Conversely, the model group exhibited a thicker keratinized layer and reduced dermal thickness, delayed cortical secretion, and sparse collagen fiber distribution. In the healthy group, there were no significant changes in the thickness of the skin's keratinized layer and dermis, although glandular ducts expanded and secreted vigorously, and collagen fibers appeared dense and abundant.

The Fruit Acid Treatment Alleviated the Oxidative Stress Response in the Skin Tissues Induced by Ultraviolet Radiation

In comparison to the healthy group, the levels of SOD activity, CAT, and GSH-Px in mouse skin tissues of the Model group were significantly reduced ($p < 0.01$, and $p < 0.001$) (Fig. 2A,B,D). Conversely, compared to the Model group, the fruit acid treatment group exhibited a noticeable increase in SOD activity, CAT, and GSH-Px levels ($p < 0.05$, and $p < 0.01$) (Fig. 2A,B,D). Additionally, the MDA level in the Model group was significantly higher than that in the healthy group ($p < 0.001$) (Fig. 2C). Following fruit acid treatment, the MDA level was markedly reduced compared to the Model group ($p < 0.001$) (Fig. 2C).

The Fruit Acid Treatment Alleviated the Inflammatory Response in Skin Tissues Induced by Ultraviolet Radiation

Compared to the healthy group, the levels of IL-6, TNF-α, IL-1β, and IFN-γ were significantly elevated in the Model group ($p < 0.001$) (Fig. 3A–D). In contrast, com-

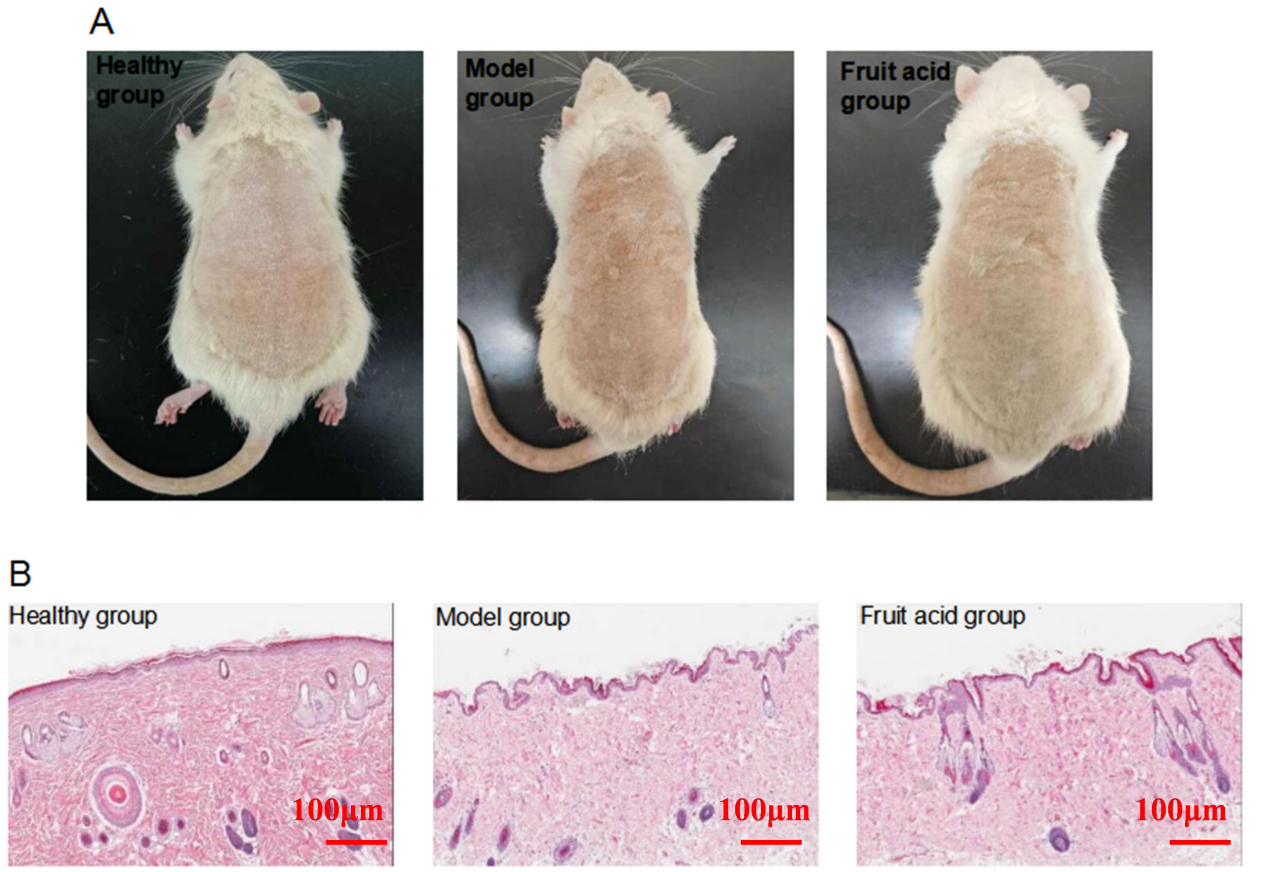

Fig. 1. The fruit acid treatment alleviated skin damage and aging induced by ultraviolet radiation. (A) Photograph of the dorsal skin of the health group, fruit acid group and model set rats was taken for phenotype analysis. (B) Hematoxylin-eosin (HE)-stained histological image of skin tissue section of health group, fruit acid group and model rats was captured and rats skin photoaging model construction. Scale bar = 100 μm. n = 6.

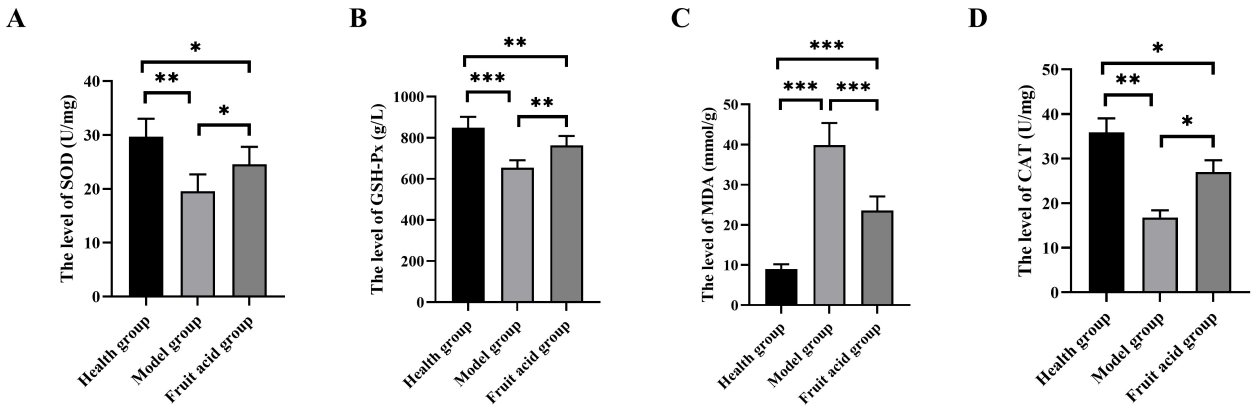

Fig. 2. The application of fruit acid treatment mitigated the oxidative stress response in skin tissues induced by ultraviolet radiation. (A–D) Determine (A) Superoxide Dismutase (SOD) activity, (B) Glutathione Peroxidase (GSH-Px), (C) Malondialdehyde (MDA), and (D) Catalase (CAT) levels in different treatment groups through Enzyme-Linked Immunosorbent Assay (ELISA). n = 6. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

pared to the Model group, the fruit acid treatment group exhibited a notable reduction in the levels of IL-6, TNF-α, IL-1β, and IFN-γ ($p < 0.001$) (Fig. 3A–D).

The Fruit Acid Treatment Rescued the Decreased Expression of Collagen Induced by Ultraviolet Radiation in Skin Tissues

We conducted Western blot experiments to analyze the expression differences of collagen and elastin proteins in

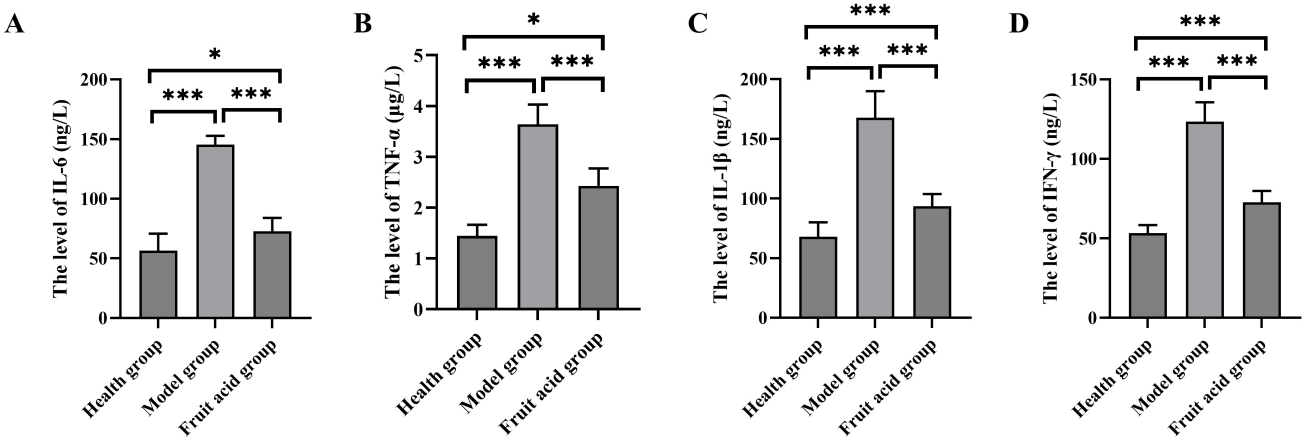

Fig. 3. The application of fruit acid treatment mitigated the inflammation in skin tissues triggered by ultraviolet radiation. (A–D) The levels of Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), IL-1β, and Interferon-gamma (IFN-γ) in different groups using ELISA. n = 6. *$p < 0.05$, ***$p < 0.001$.

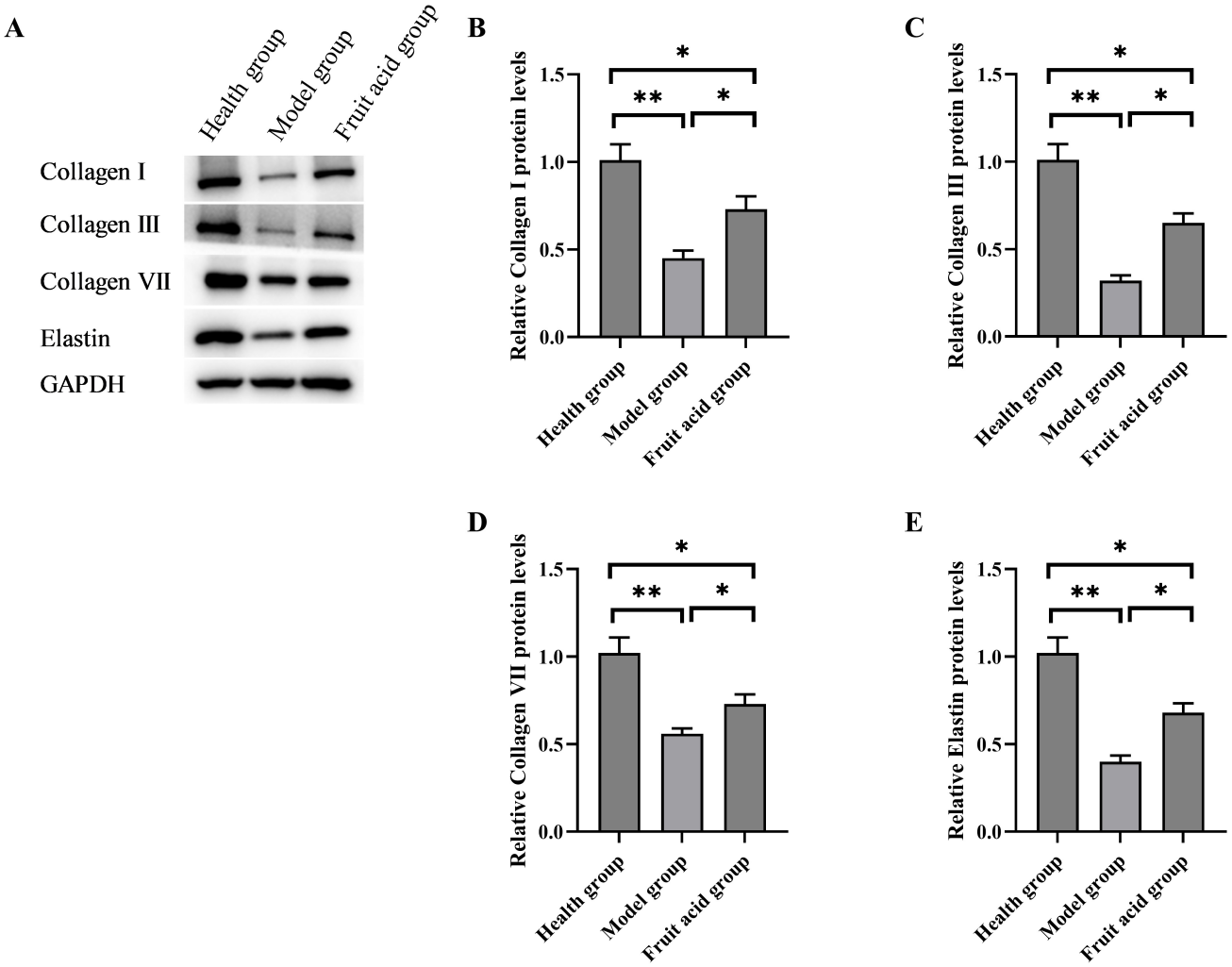

Fig. 4. Differences in the expression of collagen and elastin proteins in skin tissues among different groups. (A–E) The protein band (A) and expression levels of Collagen I (B), Collagen III (C), Collagen VII (D), and elastin (E) in different treatment groups. n = 6. *$p < 0.05$, **$p < 0.01$. GAPDH, Glyceraldehyde 3-phosphate dehydrogenase.

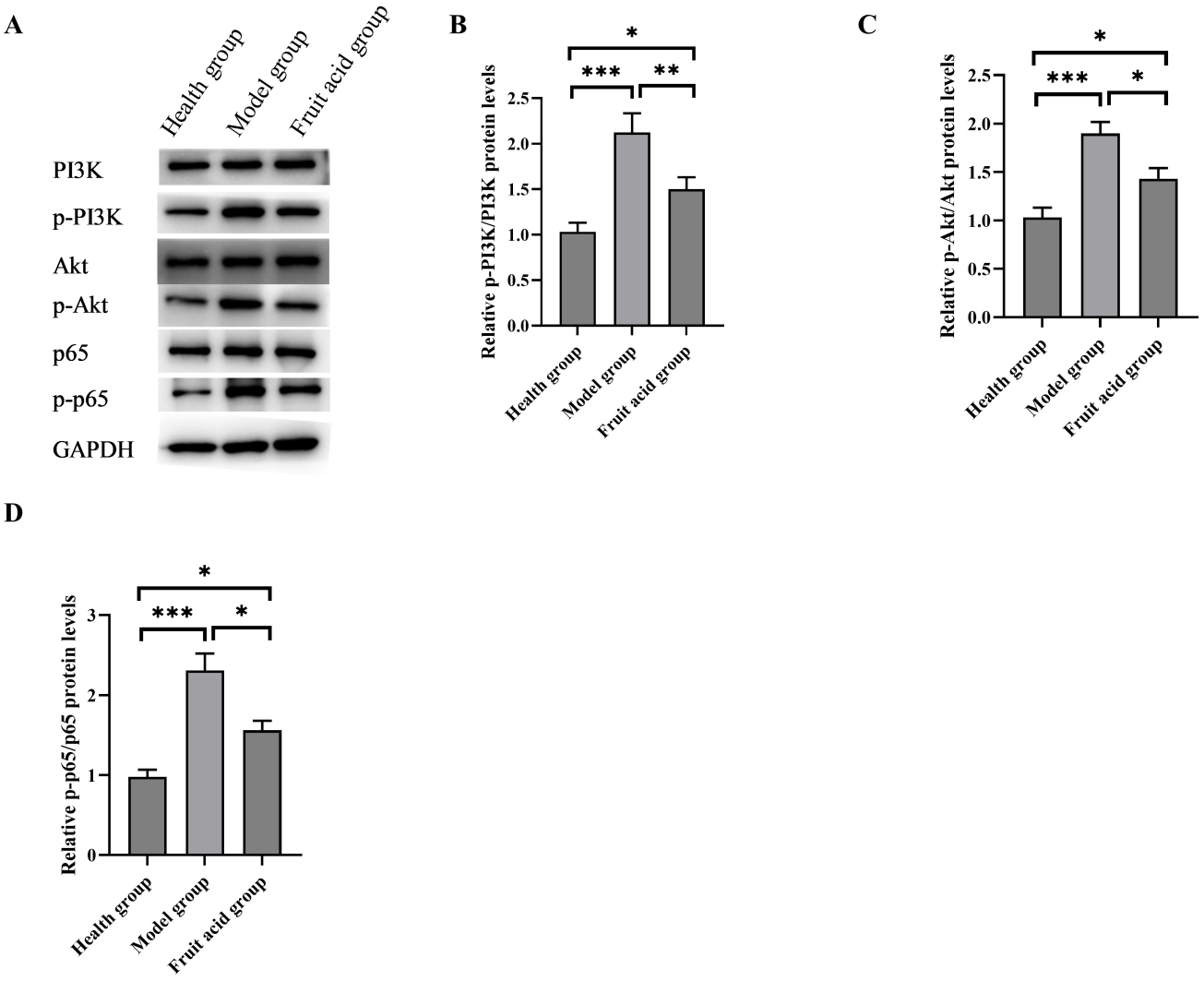

Fig. 5. The application of fruit acid treatment is capable of suppressing the activation of the PI3K/Akt and NF-κB signaling pathways induced by ultraviolet exposure. (A–D) The protein expression levels of PI3K, p-PI3K, Akt, p-Akt, p65, p-p65 in skin tissues using Western blot analysis. n = 6. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. PI3K, Phosphoinositide 3-kinase; p-PI3K, Phosphorylated PI3K; Akt, Protein Kinase B; p-Akt, Phosphorylated Akt; p-p65, Phosphorylated p65; NF-κB, Nuclear Factor kappa B.

different groups. Compared to the healthy group, the expression levels of Collagen I, Collagen III, Collagen VII, and elastin were significantly reduced in the Model group ($p < 0.01$) (Fig. 4A–E). However, following fruit acid treatment, there was a significant increase in the expression levels of Collagen I, Collagen III, Collagen VII, and elastin in the skin tissues compared to the Model group ($p < 0.05$) (Fig. 4A–E).

Fruit Acid Treatment Inhibited the Ultraviolet-Induced Activation of the PI3K/Akt and NF-κB Signaling Pathways

Subsequently, we investigated whether ultraviolet exposure induced activation of the PI3K/Akt and NF-κB signaling pathways in skin tissues. The results confirmed that, in comparison to the healthy group, the levels of p-PI3K, p-Akt, and p-p65 expression were significantly elevated in the skin tissues of the Model group ($p < 0.001$) (Fig. 5A–D). However, after fruit acid treatment, there was a noticeable reduction in the levels of p-PI3K, p-Akt, and p-p65 expression in mouse skin tissues compared to the Model group ($p < 0.05$, and $p < 0.01$) (Fig. 5A–D). Notably, the protein expression levels of PI3K, Akt, and p65 showed no significant differences among the healthy, Model, and fruit acid treatment groups.

Discussion

The characteristics of photoaging skin, such as epidermal hyperplasia, dermal elastic hyperplasia, collagen degradation, and inflammatory infiltration, can be observed under the microscope [9]. Oxidative damage and inflammatory damage induced by ultraviolet light have been confirmed to play an important role in the pathogenesis of pho-

toaging [10]. SOD and MDA can accurately reflect the degree of oxidative stress damage to the body to a certain extent [11]. An abnormal increase in MDA exacerbates oxidative damage and worsens the patient's condition, while high expression of SOD, CAT, and GSH-Px can effectively reduce oxidative stress responses in the body and control the disease condition [12].

In this study, the levels of SOD, CAT, and GSH-Px in the serum of the hydroxy acid group and the healthy group were significantly increased, while the levels of MDA were significantly decreased. This further indicates that hydroxy acid treatment could significantly reduce the degree of oxidative stress injury in rats with skin photoaging. The main mechanism of action is likely that the oxidative antioxidant system balance is disrupted under prolonged exposure to ultraviolet radiation, leading to deep oxidative stress reactions in the skin, thereby damaging skin cells and causing premature aging. Fruit acid can rapidly eliminate the accumulation of a large number of oxygen free radicals in the body, thereby reducing the risk of accumulation of oxidative products and damage, and inhibiting oxidative stress reactions. This can effectively reduce MDA levels and increase SOD, CAT, and GSH-Px levels, which is beneficial for promoting disease control and prognosis [13].

The results of this study demonstrate that the inflammatory cytokines IL-6, IL-1β, IFN-γ, and TNF-α in the levels of the fruit acid and healthy groups were significantly lower than those in the model group, consistent with previous findings [14]. This suggests that fruit acid treatment can inhibit inflammatory reactions associated with skin aging in rats. It is speculated that this may be due to the accumulation of reactive oxygen species in the body caused by external radiation, which further activates NF-κB. This process accelerates the activation of NF-κB and phosphorylation of p65, promoting the synthesis of IL-6, IL-1β, IFN-γ, TNF-α, and other proinflammatory cytokines, and inducing necrosis and apoptosis of skin cells. This cascade of events can lead to the degradation of extracellular matrix components, resulting in skin laxity, wrinkles, erythema, and ultimately, photoaging. The application of hydroxy acid treatment can intervene by eliminating the accumulation of oxygen free radicals, thereby reducing the inflammatory reactions triggered by reactive oxygen species accumulation, and subsequently decreasing the levels of proinflammatory factors [14,15].

The primary symptom of human aging manifests as skin wrinkles, predominantly attributed to collagen loss. Collagen content in the dermis is notably high, and as age advances, there is a significant decrease in collagen levels, leading to diminished skin firmness and elasticity. Collagen, constituting more than 10% of amino acids in the body, demonstrates high stability, and its fluctuations indirectly reflect changes in collagen content and skin aging [16]. Skin photoaging is characterized by thinning of the epidermal keratin layer, thickening of the dermis, increased collagen fiber density, and heightened secretion activity. According to the study findings, the fruit acid treatment group exhibited significantly increased levels of type I collagen, type III collagen, type VII collagen, and elastin in mouse skin tissues compared to the model group.

This provides additional confirmation that fruit acid treatment enhances the restoration of skin luminosity following collagen aging, effectively improving skin wrinkles, pigmentation, and other symptoms. The main mechanism involves the strong permeability of fruit acid, enabling it to quickly penetrate the skin's cutin layer upon application and be absorbed rapidly. Simultaneously, it interferes with the binding forces on the cell surface, reducing cutin cell adhesion and promoting skin restoration, thereby effectively reducing pigmentation. Additionally, hydroxy acid can facilitate skin exfoliation and promote the regeneration of new skin, which is beneficial for improving skin lesions associated with photoaging and enhancing treatment efficacy [17,18].

Herein, we establish that the application of fruit acid treatment effectively hampers the activation of the PI3K/Akt and NF-κB signaling pathways triggered by exposure to ultraviolet light. The PI3K/Akt pathway holds pivotal significance in governing cellular survival, proliferation, and metabolic regulation. Fruit acid treatment appears to impede PI3K activation, consequently obstructing Akt phosphorylation and diminishing the overall activity of this pathway. This inhibition may lead to heightened apoptosis and a deceleration in cell proliferation, thereby contributing to the maintenance of robust skin tissue. NF-κB serves as a crucial regulator in the inflammatory response and is intricately involved in modulating cellular inflammatory reactions. Ultraviolet exposure conventionally induces the activation of the NF-κB pathway, setting off inflammatory responses. The impact of fruit acid treatment likely involves the suppression of NF-κB's transcriptional activity, resulting in a reduction in the expression of genes associated with inflammation and subsequently mitigating skin inflammation induced by UV exposure. Insights from research on the inflammatory response during the skin photoaging process suggest that the immune system, inflammation, and coagulation are concurrently stimulated as protective mechanisms against potential harmful stimuli [19,20].

In the context of chronological and externally induced skin aging, both Akt and NF-κB activation demonstrate an increase, but inhibition of Akt activity *in vivo* has been observed to decrease NF-κB activation [21,22]. In summary, fruit acid treatment exhibits potential to alleviate skin damage caused by ultraviolet radiation through a multifaceted approach, encompassing the inhibition of key signaling pathways, antioxidant properties, and modulation of gene expression.

There are still some shortcomings and deficiencies in this research. For instance, the rat model utilized to simulate skin aging did not specifically target the analysis of

acidity daub dose, which resulted in an imperfect study design. Therefore, further research should focus on evaluating the effect of different concentrations of fruit acid treatment on oxidative stress, inflammatory factors, and collagen indices in light skin aging rats. Additionally, the PI3K/Akt and NF-κB signaling axis could serve as a potential therapeutic target for managing inflammation in skin photoaging.

Conclusion

In summary, fruit acid treatment has been found to mitigate the oxidative stress response, suppress the secretion of inflammatory factors, and facilitate collagen recovery, thereby ameliorating symptoms associated with skin photoaging in rats. The underlying mechanism appears to involve the inhibition of the PI3K/Akt and NF-κB signaling pathways.

Availability of Data and Materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

BW: conception, design, materials, data collection, analysis, literature review, writing. JD: design, materials, analysis, literature review, writing. FL: supervision, data collection, analysis, literature review, writing. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Ethical approval for this study was obtained from the Medical Ethics Committee of Beijing Chaoyang Hospital Affiliated with Capital Medical University (Approval No.: 2023-126).

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Conflict of Interest

The authors declare no conflict of interest.

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