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In vitro and in vivo exploration of microbiome-derived yeast extract for anti-aging and skin rejuvenation

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Abstract

Background Skin aging, a multifactorial process driven by intrinsic and extrinsic factors, results in diminished hydration, elasticity, and increased wrinkle formation. Yeast extract, particularly from *Saccharomyces cerevisiae (S. cerevisiae*), is rich in bioactive compounds with potential anti-aging properties, but its effect via oral administration remains underexplored.

Objective To evaluate the anti-aging efficacy of glutathione-enriched *S. cerevisiae* yeast extract in a photoaging-induced mouse model and human skin cell lines, including fibroblasts and keratinocytes, focusing on its molecular mechanisms.

Methods In vitro studies were conducted using human dermal fibroblasts and keratinocytes to assess antioxidant activities of yeast extract (SOD and GPx), inflammatory markers (IL-1β, IL-6, TNF-α, and COX-2), and effects on aging-associated factors such as collagen, elastin, hyaluronic acid production and matrix metalloproteinase (MMP), collagenase, elastase, hyaluronidase activities. For in vivo studies, SKH-1 hairless mice were exposed to UVB irradiation to induce photoaging and orally administered yeast extract at various doses. Skin improvements were evaluated through measurements of hydration, trans-epidermal water loss (TEWL), elasticity, collagen fiber density, roughness, and epidermal thickness.

Results The yeast extract exhibited significant anti-aging effects in both in vitro and in vivo models. In vitro, it upregulated collagen and elastin synthesis, enhanced hyaluronic acid content, promoted antioxidant enzymes, and lessened inflammatory markers. Additionally, key dermal degradation factors, including MMP, elastase, collagenase, and hyaluronidase, were significantly downregulated. In vivo, oral administration improved skin hydration, TEWL, elasticity, and collagen fiber density, while visibly reducing wrinkle depth and roughness. Histological analysis further confirmed decreased epidermal thickness and increased collagen deposition, highlighting the extract's potential in skin rejuvenation.

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Conclusions Glutathione-enriched *S. cerevisiae* yeast extract showed substantial promise as a multifunctional anti-aging agent. It enhanced skin hydration, reduced oxidative stress, mitigated inflammation, and improved structural integrity, offering a comprehensive approach to combat skin aging.

Keywords *Saccharomyces cerevisiae*, Yeast extract, Glutathione, Anti-aging, Antioxidants, Photoaging, Skin health

Introduction

As the aesthetics and dermatological industries continue to advance in search of innovative anti-aging interventions, plant- and microbiome-derived extracts have emerged as promising candidates for skin rejuvenation. A growing body of laboratory-based research has evaluated a diverse array of these natural agents. For instance, *Allium pseudojaponicum* extract has been shown to exert photoprotective and hydration-enhancing effects on keratinocytes, while quercetin and tanshinone—bioactive compounds isolated from the traditional Chinese medicinal plant *Cuscuta chinensis*—have demonstrated potent antioxidative and anti-aging properties [1, 2]. Beyond botanicals, microbe-derived products are also gaining traction. Specifically, *Lactiplantibacillus plantarum* has been applied in the management of various forms of alopecia, and numerous yeast-derived extracts have been incorporated into skin-care formulations due to their potential dermo-cosmetic benefits [3–5].

Among these, *Saccharomyces cerevisiae (S. cerevisiae)*, widely known as brewer's or baker's yeast and a natural constituent of the human gut microbiota, is particularly rich in antioxidant bioactives, including β-glucan, mannan, selenium, amino acids, vitamins, and most prominently, glutathione—a key intracellular antioxidant with significant relevance to skin health [5–8]. The application of this microorganism and its extract has been studied in numerous aspects of dermatology, such as the enhancement of hair, nail, and skin health. The topical application of *S. cerevisiae* extract, combined with other vitamins, can enhance skin moisture and attenuate skin roughness over time [9]. The yeast extract also displayed superior itch-reducing features compared to colloidal oatmeal [10]. Healing enhancement in burn wounds was also observed after topical usage of *S. cerevisiae* in a mouse model [11]. Its cell wall components have also enabled the development of a sunscreen containing gelatin and yeast, showing excellent ultraviolet (UV) protection in vitro and in vivo [12]. Remarkably, *S. cerevisiae* extract also managed to inhibit melanoma proliferation [13]. In animal studies, the oral intake of *S. cerevisiae* increased digestibility, gut microbiota, and activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase [14]. As an acknowledgment of its utility and safety, the Korean Ministry of Food and Drug Safety has permitted *S. cerevisiae* for food consumption [15].

Despite multiple pieces of evidence supporting its use in various aspects of skin enhancement, data regarding the oral administration of the yeast extract in treating skin aging remains scant. Therefore, we aim to assess the anti-aging efficacy of the glutathione-rich *S. cerevisiae* yeast extract in a photoaging-induced hairless mouse model. Moreover, we conducted in vitro experiments using human dermal fibroblasts (HDF) and epidermal keratinocytes (KC) to elucidate the anti-aging molecular mechanisms of the yeast extract.

Materials and methods

In vitro study on yeast extract

Test product

S. cerevisiae was extracted using 90% ethanol at 30 °C for 6 h, after which the extract was filtered, concentrated, and subjected to vacuum drying to obtain the final product, 60% of which is glutathione. Quercetin (QC; PHR1488), retinoic acid (RA; R2625), and ursolic acid (UA; U6753) were sourced from Sigma Aldrich (USA); 1,10-phenanthroline inhibitor (Phen) was brought from Thermo Fisher (USA).

Cell culture

HDF and KC cell lines were purchased from Thermo Fisher Scientific (USA). HDF cells were cultured in Dulbecco's Modified Eagle Medium (SH30243.01, Hyclone, USA) with 10% fetal bovine serum (26,140,079, Gibco, USA) and 1% penicillin–streptomycin (15,140–122, Gibco, USA). KC cells were maintained in EpiLife™ medium with 60 μM calcium and Human Keratinocyte Growth Supplement (S0015, Thermo Fisher, USA). Cultures were incubated at 37 °C with 5% CO_2. HDF cells (passage 7) and KC cells (passage 5) were used for experiments.

Cell cytotoxicity

The cytotoxic effects of yeast extract after UVB irradiation were assessed using the WST assay (CK04, Dojindo, Japan). Cells (5×10^3/well) were seeded in 96-well plates and cultured to approximately 80% confluence. After washing with PBS, HDF cells were exposed to 30 mJ/cm^2 UVB and KC cells to 20 mJ/cm^2 UVB using a BLX-312 UV cross-linker (Vilber Lourmat, France) at 312 nm. Post-irradiation, cells were treated with yeast extract at varying concentrations and incubated for 24 h. WST substrate was added and incubated at 37 °C for 2 h, and absorbance at 450 nm was measured using an ELISA microplate reader (VARIOSKAN LUX, Thermo Fisher Scientific, USA) to determine cell viability.

Improvement efficacy assessment

The reduction of tissue degradation of yeast extract was assessed using the EnzChek™ Gelatinase/Collagenase Assay Kit (E12055, Invitrogen, USA), N-succinyl-tri-alanyl-p-nitroanilide (S4760, Sigma Aldrich, USA), and porcine pancreas elastase (E7885, Sigma Aldrich, USA). Collagenase activity inhibition was measured via fluorescence using a microplate reader (VARIOSKAN LUX, Thermo Fisher Scientific, USA) (Excitation: 495 nm, Emission: 515 nm) after 30 min of reaction at 25 °C. Regarding elastase, yeast extract was prepared at various concentrations in 50 mM Tris–HCl buffer (pH 8.0) and distributed into 96-well plates. The reaction mixture included 1 mg/mL N-succinyl-tri-alanyl-p-nitroanilide and 0.6 U/mL porcine pancreas elastase. The reaction was incubated at 25 °C for 15 min. Absorbance was then measured at 405 nm using a microplate reader to calculate elastase activity inhibition. Phen (0.25 mM) and UA (50 µg/ml) were used as positive controls.

Effects on wrinkle-related factors in HDF cells were assessed using Collagen-1 (ab210966, Abcam, UK), Elastin (MBS704171, MyBioSource, USA), MMP-1 (ab215083, Abcam, UK), MMP-3 (MBS2500861, MyBioSource, USA), and MMP-9 (ab246539, Abcam, UK) ELISA kits. HDF cells were seeded into 6-well plates at a density of 5×10^4 cells per well. After UVB exposure (30 mJ/cm^2), yeast extract treatment, and incubation, protein levels were quantified using the BCA Protein Assay Kit. RA (1.25 µM): positive control.

The antioxidant activity of yeast extract in KC cells was evaluated using OxiTECTM SOD (BO-SOD-250, BIOMAX, South Korea) and GPx (ab102530, Abcam, UK) assay kits. Moisturizing effects on KC cells were analyzed using Human Hyaluronan (DHYAL0, R&D Systems, USA), hyaluronic acid synthase-2 (HAS-2) (MBS2882985, MyBioSource, USA), and Hyaluronidase-1 (MBS1603542, MyBioSource, USA) ELISA kits. The anti-inflammatory properties of yeast extract were assessed using Human Interleukin (IL)–1 beta (ab214025, Abcam, UK), Human IL-6 (ab178013, Abcam, UK), Human Tumor Necrosis Factor-alpha (TNF-alpha) (ab181421, Abcam, UK), and Human Cyclooxygenase-2 (COX-2) (ab267646, Abcam, UK) ELISA kits. KC cells were seeded into 6-well plates at a density of 5×10^4 cells per well. Upon reaching approximately 80% confluence, cells were exposed to 20 mJ/cm^2 UVB, treated with yeast extract, incubated for 24 h, then harvested for protein quantification. QC (12.5 µM): positive control.

All experiments were performed in triplicate, and averages were recorded.

In vivo study on yeast extract

Photoaging-induced animal model

Five-week-old female SKH-1 hairless mice (Dual MPA580) were purchased from RaonBio Co., Ltd. (Yongin, South Korea), a certified supplier for research animals, and all necessary approvals and documentation were obtained prior to the study. All mice were acclimated for one week under controlled conditions (24 °C ± 0.5 °C, 55% – 65% humidity, 12-h light/dark cycle) with free access to feed. Experimental procedures were approved by the Institutional Animal Care and Use Committee (Approval number: Hulux-2024–06-001) and conducted in compliance with ethical guidelines (the AVMA Guidelines for the Euthanasia of Animals (2020 edition) [16]).

Mice were divided into six groups after acclimation. Following isoflurane anesthesia, the dorsal skin of experimental groups (excluding the non-irradiated control) was exposed to UVB irradiation at 50 mJ/cm^2/day in week one, increasing by 50 mJ/cm^2/day each week for eight weeks, three times weekly.

Distilled water was orally administered to the negative control group. The test product, yeast extract, was dissolved in distilled water and administered orally to the experimental groups at doses of 50, 100, and 150 mg/kg/day. Ascorbic acid (A92902, Sigma Aldrich, USA) at 100 mg/kg/day served as the positive control. All treatments were administered five times weekly following UVB exposure, while conventional feed was provided separately. Body weight was monitored weekly to assess any changes.

All mice were sacrificed using carbon dioxide (CO_2) asphyxiation in accordance with the AVMA Guidelines for the Euthanasia of Animals (2020 edition) [16]. CO_2 was introduced into the chamber gradually at a displacement rate of 30–70% of the chamber volume per minute to minimize distress, as recommended by the guidelines. The mice were monitored continuously, and death was confirmed by cessation of respiratory and cardiac activity. This method was chosen as it is widely recognized for its effectiveness and minimal distress to the animals.

Skin improvement efficacy assessment

Skin elasticity was measured using a Cutometer (Dual MPA580, Courage + Khazaka, Germany) with negative pressure (300 mbar), setting suction and relaxation times to 2 s each in three cycles. Higher parameter R2 values indicate better elasticity. Skin moisture was assessed with a Corneometer (CM825, Courage + Khazaka, Germany) via capacitance differences. The measurement unit is AU (Arbitrary Unit), and higher values indicate improved skin hydration. Using a Tewameter (TM300, Courage + Khazaka, Germany), trans-epidermal water loss (TEWL) was measured for 30 s, with lower

values reflecting improved barrier function. Moreover, Skin roughness (parameter R3) was evaluated using a Visioscan (VC98, Courage + Khazaka, Germany), where smaller R3 values indicate smoother skin.

To evaluate epidermal thickness, skin tissues were fixed in 10% formalin for over 24 h, processed into paraffin blocks, and paraffin-embedded slides. Deparaffinized tissues were stained with hematoxylin (S3309, Dako, Denmark) for nuclei and eosin (318,906, Sigma Aldrich, USA) for cytoplasm, then dehydrated and mounted. The epidermis and papillary dermis were imaged at 400 × magnification using an optical microscope (BX43F, Olympus, Japan), and thickness was measured using the ImageJ program (National Institutes of Health, USA). Increased epidermal thickness indicated skin photoaging.

To assess collagen fiber production via Masson's Trichrome staining, tissues fixed in 10% formalin for over 24 h were processed into paraffin blocks and slides. After deparaffinization, tissues were stained using Bouin's solution (2010, BBC Biochemical, USA), Weigert's iron hematoxylin (hematoxylin: 4077–4425, Daejung, South Korea/ ferric chloride: 660, Duksan, South Korea) for nuclei, Biebrich Scarlet Acid Fuchsin (Biebrich Scarlet: B6008, Sigma Aldrich, USA/Acid Fuchsin: 4048–4125, Daejung, South Korea) for cytoplasm and muscle fibers, and aniline blue (1087–4125, Daejung, South Korea) for collagen fibers, with intermediate rinsing and decolorization steps. Aniline was removed with acetic acid, and tissues were dehydrated and mounted. Collagen fiber density (%) was calculated by measuring the area of collagen fibers (stained blue) relative to the total papillary dermis area using an optical microscope (400x, BX43F, Olympus) and image analysis software (Zen, Zeiss).

Protein biomarkers for aging [Mouse MMP-3 (ab203363, Abcam, UK)] and moisture enhancement [Mouse hyaluronic acid (HA) (MBS705186, MyBioSource, USA), Mouse HAS-2 (MBS761832, MyBioSource, USA), Mouse hyaluronidase-1 (HYAL-1) (MBS2887397, MyBioSource, USA)] were quantified via ELISA kits. Tissues were homogenized, centrifuged, and analyzed using kit protocols. Total protein content was measured with the BCA Protein Assay Kit (Sigma Aldrich).

All measurements were conducted on the dorsal skin of mice under standardized protocols and repeated three times to ensure reliability and consistency.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics 25.0 program to evaluate the significance between the experimental and control groups, with a hypothesis significance level set at 5% ($p < 0.05$). Graphing was conducted using the GraphPad Prism 10.2.2 software. After testing for normality, an independent samples t-test (parametric method) was used to determine significance based on whether the normality assumption was satisfied.

Results

In vitro effects of yeast extract on aging-associated markers

Based on cell cytotoxicity results, we selected the three yeast extract concentrations for HDF and the three test product titers for KC (Figure S1).

The current study evaluated collagenase, elastase, Collagen-1, Elastin, MMP-1, MMP-3, and MMP-9 as the biomarkers for skin aging. The results showed yeast extract significantly reduced collagenase activity, showing greater effects with increasing concentrations (control, 0 ± 0.667%; 0.025%, 8.92 ± 0.574%; 0.125%, 18.895 ± 0.709%; 0.250%, 30.367 ± 0.323%; 0.500%, 74.087 ± 0.214%; Phen, 87.393 ± 0.092%; **** $p < 0.001$; Fig. 1A). A similar trend was observed in elastase, however, statistical significance was only achieved for higher concentrations of yeast extract (control, 0 ± 2.748%; 10%, 39.387 ± 7.85%; 20%, 96.58 ± 1.081%; UA, 37.972 ± 5.597%; ****$p < 0.001$; Fig. 1B).

Collagen-1 protein expression in HDF was significantly downregulated after UVB irradiation (non-irradiated control, 189.363 ± 0.605 ng/ml; UVB-irradiated control, 44.574 ± 0.854 ng/ml, $p < 0.05$, Fig. 2A). Treatment with 100 ppm of yeast extract markedly promoted the expression of collagen-1 (100 ppm, 67.308 ± 0.353 ng/ml; RA, 81.826 ± 6.519 ng/ml; $p < 0.05$, Fig. 2A).

Elastin protein expression in HDF was significantly downregulated after UVB irradiation (non-irradiated control, 34.404 ± 0.365 pg/ml; UVB-irradiated control, 24.203 ± 0.132 pg/ml, $p < 0.05$, Fig. 2B). Treatment with yeast extract greatly increased the expression of elastin, with the most prominent effect at 100 ppm (25 ppm, 33.879 ± 1.606 pg/ml; 50 ppm, 44.983 ± 4.408 pg/ml; 100 ppm, 50.342 ± 1.235 pg/ml; RA, 34.908 ± 0.638 ng/ml; $p < 0.05$, Fig. 2B).

MMP-1 protein levels in HDF were significantly elevated after UVB irradiation (non-irradiated control, 101.616 ± 0.4 ng/ml; UVB-irradiated control, 268.725 ± 5.2 ng/ml; $p < 0.05$, Fig. 2C). Treatment with yeast extract significantly dwindled this increase, with the most prominent effect at 50 and 100 ppm (25 ppm, 107.85 ± 0.744 ng/ml; 50 ppm, 67.06 ± 1.04 ng/ml; 100 ppm, 76.264 ± 1.34 ng/ml; RA, 40.176 ± 0.907 ng/ml; $p < 0.05$, Fig. 2C).

A similar trend to MMP-1 was recorded for MMP-3 (non-irradiated control, 47.933 ± 0.078 ng/ml; UVB-irradiated control, 98.855 ± 0.324 ng/ml; 25 ppm, 34.385 ± 0.455 ng/ml; 50 ppm, 25.952 ± 0.159 ng/ml; 100 ppm, 10.252 ± 0.253 ng/ml; RA, 40.176 ± 0.907 ng/ml; $p < 0.05$, Fig. 2D) and MMP-9 (non-irradiated

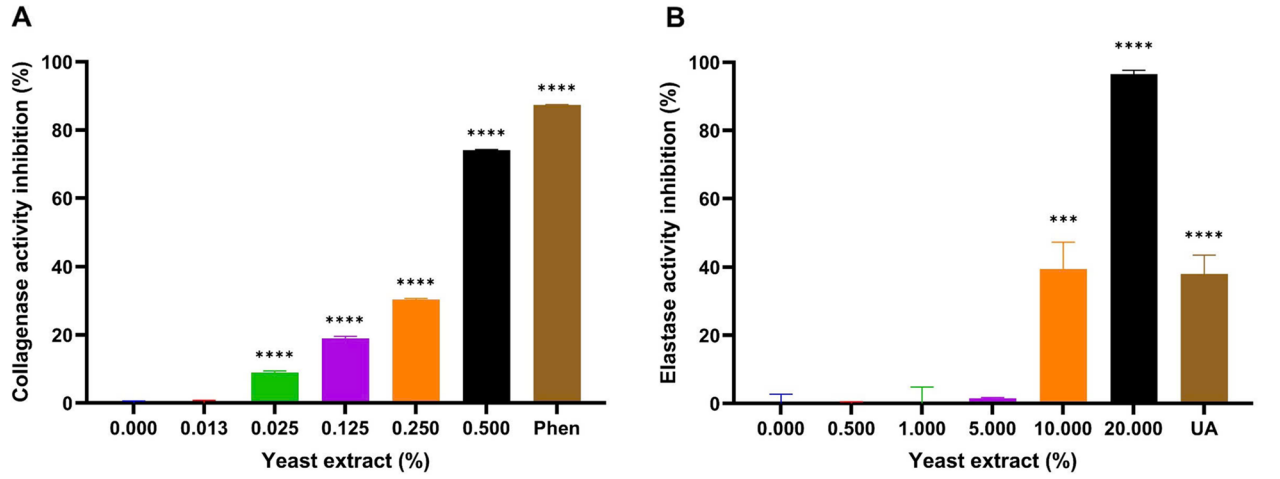

Fig. 1 Effects of yeast extract on collagenase and elastase activity. Yeast extract effectively inhibited the activity of collagenase at 0.025, 0.125, 0.250, and 0.500% concentrations (**A**). It also reduced elastase activity at 10.000 and 20.000% concentrations (**B**). Phen, (1,10)-Phenanthroline, 0.25 mM; UA, Ursolic acid, 50 μg/ml; ***$p < 0.005$, ****$p < 0.001$, independent samples t-test compared to the control group. The error bars are based on standard deviation

control, 22.755 ± 0.878 ng/ml; UVB-irradiated control, 64.617 ± 0.203 ng/ml; 25 ppm, 11.317 ± 0.638 ng/ml; 50 ppm, 6.588 ± 0.853 ng/ml; 100 ppm, 7.969 ± 0.555 ng/ml; RA, 40.176 ± 0.907 ng/ml; $p < 0.05$, Fig. 2E) when treating HDF with yeast extract.

In vitro antioxidant properties of the yeast extract

To evaluate the protective antioxidant effects of yeast extract, SOD and GPx activities were measured, as these are key enzymes in mitigating oxidative stress. UVB irradiation considerably decreased SOD activity in KC (non-irradiated control, 64.061 ± 1.669%; UVB-irradiated control, 54.576 ± 1.894%, $p < 0.05$, Fig. 3A), and yeast extract significantly reversed this effect (400 ppm, 62.325 ± 3.026%; 1700 ppm, 66.399 ± 3.171%; 3000 ppm, 64.93 ± 3.181%; QC, 62.592 ± 1.862%; $p < 0.05$, Fig. 3A).

Exposure to UVB also greatly diminished GPx activity in KC (non-irradiated control, 189.835 ± 1.453%; UVB-irradiated control, 133.271 ± 0.218%, $p < 0.05$, Fig. 3B), and yeast extract successfully countered this process (400 ppm, 196.023 ± 0.366%; 1700 ppm, 187.626 ± 0.393%; 3000 ppm, 192.848 ± 0.228%; QC, 180.07 ± 0.177%; $p < 0.05$, Fig. 3B).

In vitro anti-inflammatory function of yeast extract

IL-1β protein levels in KC were significantly elevated after UVB irradiation (non-irradiated control, 26.41 ± 6.509%; UVB-irradiated control, 65.163 ± 2.135%, $p < 0.05$, Fig. 4A), but yeast extract at 1700 ppm and 3000 ppm significantly attenuated this increase in a dose-dependent pattern (1700 ppm, 31.866 ± 2.44%; 3000 ppm, 27.839 ± 2.661%; QC, 26.174 ± 4.722%; $p < 0.05$, Fig. 4A). Meanwhile, IL-6 protein levels in KC were significantly elevated after UVB irradiation (non-irradiated control, 49.458 ± 5.732%; UVB-irradiated control, 125.852 ± 0.236%, $p < 0.05$, Fig. 4B), but yeast extract at 1700 ppm and 3000 ppm significantly attenuated this increase in a dose-dependent manner (1700 ppm, 62.636 ± 0.868%; 3000 ppm, 55.016 ± 4.315%; QC, 49.562 ± 0.496%; $p < 0.05$, Fig. 4B).

Moreover, TNF-α protein levels in KC were significantly elevated after UVB irradiation (non-irradiated control, 6.464 ± 0.267%; UVB-irradiated control, 104.424 ± 10.413%; $p < 0.05$, Fig. 4C), but yeast extract at 1700 ppm and 3000 ppm significantly attenuated this increase in a dose-dependent pattern (1700 ppm, 75.064 ± 4.837%; 3000 ppm, 60.902 ± 2.539%; QC, 7.74 ± 1.004%; $p < 0.05$, Fig. 4C). Lastly, COX-2 protein levels in KC were significantly elevated after UVB irradiation (non-irradiated control, 597.703 ± 41.497%; UVB-irradiated control, 755.523 ± 32.918%, $p < 0.05$, Fig. 4D), but yeast extract at 1700 ppm and 3000 ppm significantly attenuated this increase in a dose-dependent pattern (1700 ppm, 674.849 ± 29.806%; 3000 ppm, 635.815 ± 16.069%; QC, 683.021 ± 14.699%; $p < 0.05$, Fig. 4D).

In vitro effects of yeast extract on skin moisture biomarkers

The expression of HA, a key biomarker for skin hydration, was significantly reduced in KC after UVB irradiation (non-irradiated control, 58.685 ± 1.352 ng/ml; UVB-irradiated control, 40.313 ± 1.207 ng/ml; $p < 0.05$, Fig. 5A). Treatment with yeast extract significantly increased HA expression (400 ppm, 47.136 ± 1.005 ng/ml; 1700 ppm, 43.618 ± 0.584 ng/ml; 3000 ppm, 52.698 ± 1.757 ng/ml; QC, 58.199 ± 4.748 ng/ml; $p < 0.05$, Fig. 5A).

Similarly, the expression of HAS-2, a crucial enzyme involved in HA production, was markedly reduced following UVB exposure (non-irradiated

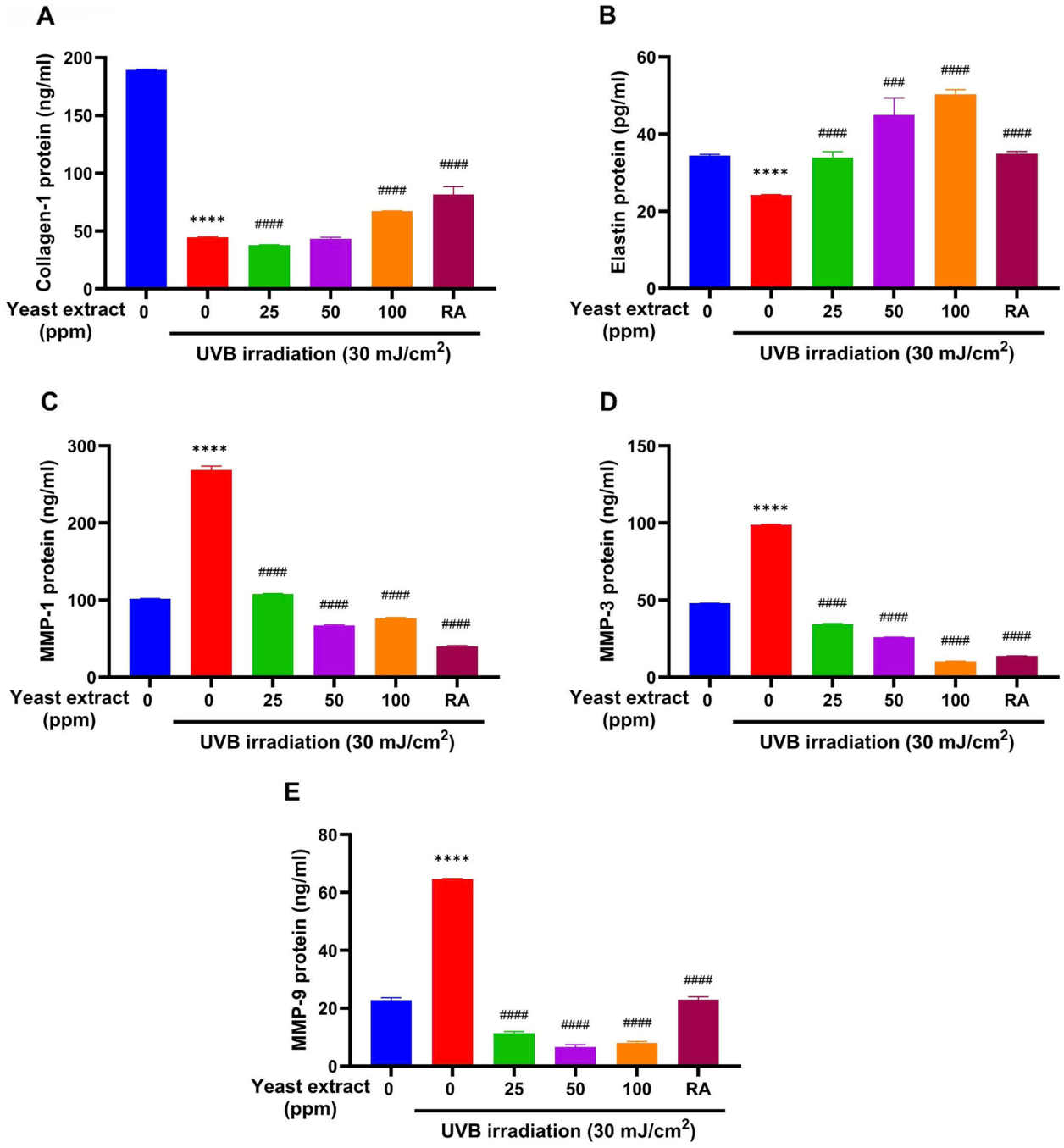

Fig. 2 Effects of yeast extract on wrinkle-related protein expression in HDF. Collagen-1 (**A**) and elastin (**B**) protein levels were significantly reduced after UVB irradiation, and yeast extract reversed this effect. On the other hand, UVB exposure enhanced the protein expression of MMP-1 (**C**), MMP-3 (**D**), and MMP-9 (**E**), but yeast extract successfully countered these influences. MMP, matrix metalloproteinase; RA, Retinoic acid, 1 μM; UVB, ultraviolet B. ****$p < 0.001$, independent samples t-test compared to non-irradiated control group; ###$p < 0.005$, ####$p < 0.001$, independent samples t-test compared to UVB-irradiated control group

control, 170.889 ± 23.111 ng/mg; UVB-irradiated control, 91.881 ± 15.373 ng/mg; $p < 0.05$, Fig. 5B). Yeast extract significantly enhanced HAS-2 expression, with higher concentrations showing greater improvements (400 ppm, 143.142 ± 8.623 ng/mg; 1700 ppm, 198.764 ± 2.178 ng/mg; 3000 ppm, 202.234 ± 10.76 ng/mg; QC, 160.812 ± 6.216 ng/mg; $p < 0.05$, Fig. 5B).

Conversely, the levels of HYAL-1, an enzyme responsible for HA degradation, were significantly elevated after UVB irradiation (non-irradiated control, 1.028 ± 0.057 mg/g; UVB-irradiated control,

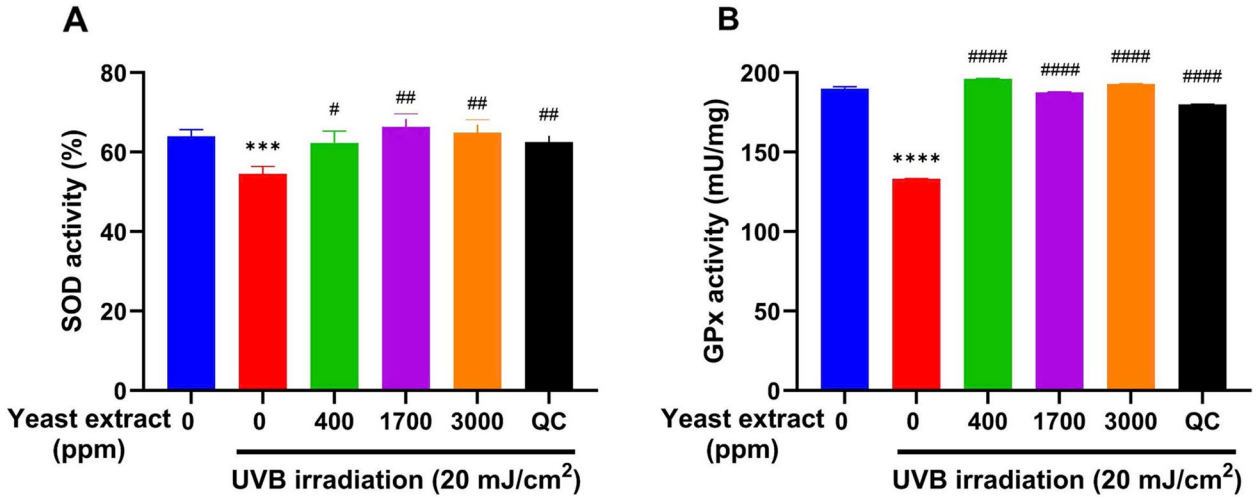

Fig. 3 Antioxidant properties of yeast extract. UVB irradiation considerably diminished the activities of antioxidants SOD (**A**) and GPx (**B**), and yeast extract successfully restored them in KC. SOD, superoxide dismutase; GPx, glutathione peroxidase; QC, Quercetin, 12.5 μM; UVB, ultraviolet B.***$p < 0.005$, ****$p < 0.001$, independent samples t-test compared to non-irradiated control group; #$p < 0.05$, ##$p < 0.01$, ####$p < 0.001$, independent samples t-test compared to UVB-irradiated control group

2.716 ± 0.161 mg/g; $p < 0.05$, Fig. 5C). Yeast extract treatment effectively reduced HYAL-1 levels (400 ppm, 2.077 ± 0.074 mg/g; 1700 ppm, 2.212 ± 0.033 mg/g; 3000 ppm, 2.018 ± 0.092 mg/g; QC, 2.171 ± 0.055 mg/g; $p < 0.05$, Fig. 5C). This demonstrates that yeast extract positively modulates key biomarkers associated with skin moisture, suggesting its potential role in improving skin hydration under UVB-induced stress.

In vivo anti-wrinkle effects of yeast extract

Skin surface images at 4 and 8 weeks following yeast extract intake in photoaging-induced mice are shown in Fig. 6A. The control group exposed to UVB exhibited prominent wrinkle formation, whereas dietary treatment with yeast extract noticeably reduced wrinkles in a dose-dependent manner, with higher doses yielding greater improvements (Fig. 6A).

Histopathological analysis of skin tissue biopsies from photoaging-induced mice is presented in Fig. 6B. UVB irradiation significantly reduced the staining density of dermal collagen fibers (non-irradiated control, 77.576 ± 2.509%; UVB-irradiated control, 61.163 ± 2.315%; $p < 0.05$, Fig. 6C). Oral administration of yeast extract for 8 weeks markedly increased collagen fiber density, with higher doses producing more pronounced enhancements (50 mg/kg/day, 65.909 ± 3.414%; 100 mg/kg/day, 75.646 ± 2.877%; 150 mg/kg/day, 75.891 ± 5.585%; AA, 78.626 ± 1.93%; $p < 0.05$, Fig. 6C).

Consistent with the in vitro findings, yeast extract intake significantly reduced the UVB-induced increase in MMP-3 protein levels after 8 weeks (non-irradiated control, 1447.004 ± 168.444 ng/g; UVB-irradiated control, 3591.154 ± 509.373 ng/g; 50 mg/kg/day, 2948.851 ± 432.222 ng/g; 100 mg/kg/day, 2436.819 ± 303.05 ng/g; 150 mg/kg/day, 2256.421 ± 302.037 ng/g; AA, 2250.552 ± 267.356 ng/g; $p < 0.05$, Fig. 6D).

UVB exposure also significantly reduced skin elasticity after 4 weeks (non-irradiated control, 0.541 ± 0.018; UVB-irradiated control, 0.398 ± 0.034; $p < 0.05$, Fig. 6E). Treatment with yeast extract effectively restored elasticity in a dose-dependent manner (50 mg/kg/day, 0.581 ± 0.032; 100 mg/kg/day, 0.64 ± 0.026; 150 mg/kg/day, 0.707 ± 0.038; AA, 0.731 ± 0.041; $p < 0.05$, Fig. 6E). A similar pattern was observed after 8 weeks (non-irradiated control, 0.545 ± 0.018; UVB-irradiated control, 0.283 ± 0.032; 50 mg/kg/day, 0.381 ± 0.029; 100 mg/kg/day, 0.412 ± 0.03; 150 mg/kg/day, 0.453 ± 0.019; AA, 0.392 ± 0.033; $p < 0.05$, Fig. 6F). Body weight measurements taken at weekly intervals are presented in Figure S2. After 8 weeks, there were no significant differences in body weight among the groups.

In vivo improvement in skin moisture of yeast extract

After 8 weeks of yeast extract consumption, hyaluronic acid levels were dose-dependently enhanced in photoaging-induced mice, as opposed to the decrease seen in UVB-irradiated control mice (non-irradiated control, 2.4 ± 0.41 μg/g; UVB-irradiated control, 1.305 ± 0.198 μg/g; 50 mg/kg/day, 3 ± 0.221 μg/g; 100 mg/kg/day, 3.239 ± 0.607 μg/g; 150 mg/kg/day, 3.688 ± 0.596 μg/g; AA, 3.964 ± 0.81 μg/g; $p < 0.05$, Fig. 7A).

The 8-week consumption of yeast extract successfully countered the UVB-induced diminishment of HAS-2 seen in the irradiated control mice, eliciting better

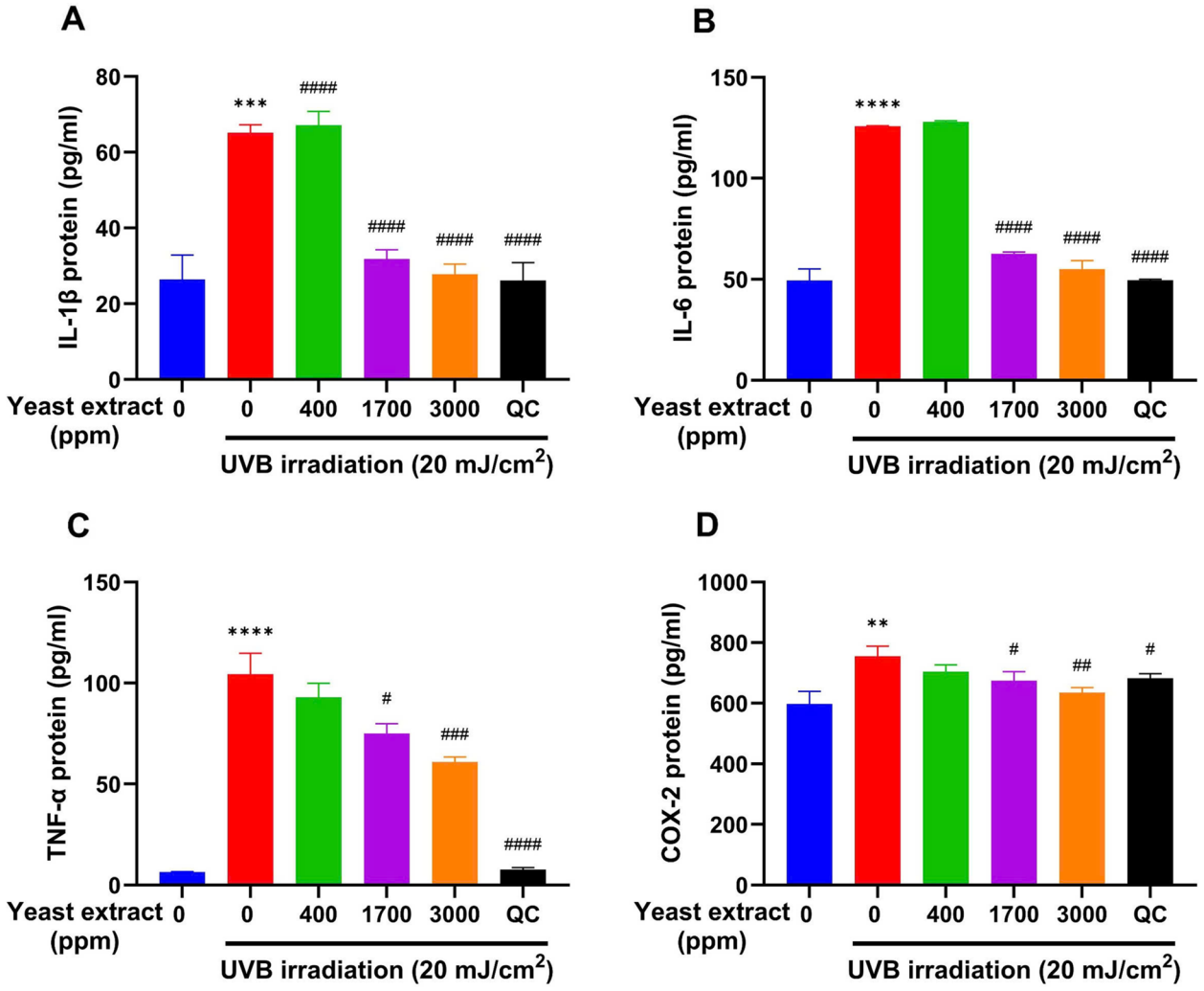

Fig. 4 Anti-inflammation properties of yeast extract. UVB treatment significantly enhanced the expression of pro-inflammatory cytokines IL-1β (**A**), IL-6 (**B**), TNF-α (**C**), and COX-2 (**D**), but yeast extract reversed this impact in KC. IL, interleukin; TNF-α, Tumor Necrosis Factor-alpha; COX-2, cyclooxygenase-2; QC, Quercetin, 12.5 μM; UVB, ultraviolet B. **$p < 0.01$, ***$p < 0.005$, ****$p < 0.001$, independent samples t-test compared to non-irradiated control group; #$p < 0.05$, ##$p < 0.01$, ###$p < 0.005$, ####$p < 0.001$, independent samples t-test compared to UVB-irradiated control group

improvements in higher concentrations (non-irradiated control, 6.259 ± 0.447 ng/g; UVB-irradiated control, 2.328 ± 0.406 ng/g; 50 mg/kg/day, 11.701 ± 1.122 ng/g; 100 mg/kg/day, 15.049 ± 1.776 ng/g; 150 mg/kg/day, 21.831 ± 2.322 ng/g; AA, 17.776 ± 2.061 ng/g; $p < 0.05$, Fig. 7B).

The intake of yeast extract reversed the UVB-induced increase in HYAL-1 observed in irradiated control mice, with bigger reductions in higher doses (non-irradiated control, 0.42 ± 0.066 μg/g; UVB-irradiated control, 1.172 ± 0.078 μg/g; 50 mg/kg/day, 0.92 ± 0.116 μg/g; 100 mg/kg/day, 0.772 ± 0.088 μg/g; 150 mg/kg/day, 0.455 ± 0.136 μg/g; AA, 0.519 ± 0.054 μg/g; $p < 0.05$, Fig. 7C).

UVB irradiation substantially increased TEWL after 8 weeks (non-irradiated control, 15.901 ± 0.346 g/h/m^2; UVB-irradiated control, 38.447 ± 4.39 g/h/m^2; $p < 0.05$, Fig. 7D). Treatment with the yeast extract diet successfully mitigated these changes (50 mg/kg/day, 29.512 ± 2.974 g/h/m^2; 100 mg/kg/day, 23.773 ± 2.095 g/h/m^2; 150 mg/kg/day, 22.838 ± 3.04 g/h/m^2; AA, 25.418 ± 2.19 g/h/m^2; $p < 0.05$, Fig. 7D).

UVB irradiation considerably decreased skin hydration after 8 weeks (non-irradiated control, 54.989 ± 2.02 AU; UVB-irradiated control, 18.883 ± 2.032 AU; $p < 0.05$, Fig. 7E). Treatment with the yeast extract diet successfully alleviated this decline (50 mg/kg/day, 28.567 ± 5.002 AU; 100 mg/kg/day, 29.322 ± 1.241 AU; 150 mg/kg/day, 33.3 ± 1.91 AU; AA, 32.684 ± 2.721 AU; $p < 0.05$, Fig. 7E).

Skin roughness and thickness improvement efficacy of yeast extract

UVB irradiation markedly increased skin roughness after 4 weeks (non-irradiated control, 20.333 ± 1.033;

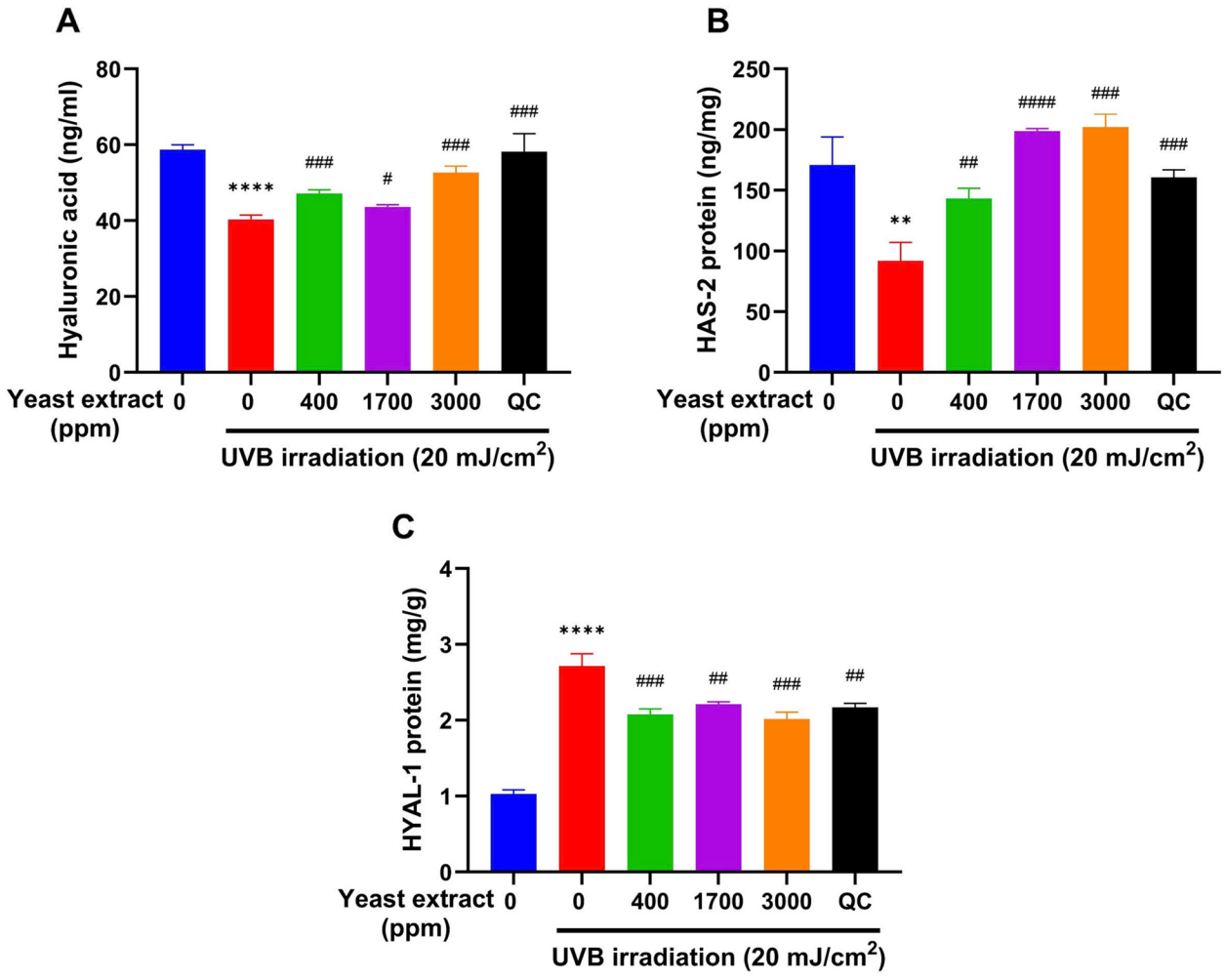

Fig. 5 Skin moisture improvement in KC by yeast extract. UVB irradiation considerably reduced hyaluronic acid (**A**), HAS-2 (**B**), and increased HYAL-1 (**C**), and yeast extract was able to counter these changes. HAS-2, hyaluronic acid synthase-2; HYAL-1, hyaluronidase-1; UVB, ultraviolet B. $^{**}p < 0.01$, $^{****}p < 0.001$, independent samples t-test compared to non-irradiated control group; $\#p < 0.05$, $\#\#p < 0.01$, $\#\#\#p < 0.005$, $\#\#\#\#p < 0.001$, independent samples t-test compared to UVB-irradiated control group

UVB-irradiated control, 28.833 ± 1.169; $p < 0.05$, Fig. 8A). Treatment with the yeast extract diet successfully reverted these changes (50 mg/kg/day, 22.5 ± 0.548; 100 mg/kg/day, 22.667 ± 0.816; 150 mg/kg/day, 21.833 ± 0.408; AA, 22.833 ± 0.753; $p < 0.05$, Fig. 8A). Skin roughness after 8 weeks observed the same trend (non-irradiated control, 20.5 ± 0.837; UVB-irradiated control, 43.5 ± 1.871; 50 mg/kg/day, 25.167 ± 2.137; 100 mg/kg/day, 24 ± 1.095; 150 mg/kg/day, 22.167 ± 0.753; AA, 24.5 ± 2.665; $p < 0.05$, Fig. 8B).

UVB irradiation significantly increased the epidermal thickness after 8 weeks (non-irradiated control, 25.565 ± 4.077 μm; UVB-irradiated control, 96.002 ± 9.729 μm; $p < 0.05$, Fig. 8C). The yeast extract diet considerably attenuated this elevation in a dose-dependent pattern (50 mg/kg/day, 81 ± 8.187 μm; 100 mg/kg/day, 79.43 ± 5.668 μm; 150 mg/kg/day, 62.811 ± 9.981 μm; AA, 59 ± 11.219 μm; $p < 0.05$, Fig. 8C).

Discussion

This study aimed to comprehensively evaluate the anti-aging properties of *S. cerevisiae* yeast extract, particularly its glutathione-enriched formulation, by investigating its effects on multiple endpoints of skin aging through in vitro and in vivo experiments. The main findings revealed that yeast extract effectively mitigates skin aging by enhancing hydration and elasticity, reducing wrinkle formation, and improving oxidative and inflammatory profiles in UVB-induced damage models. Importantly, the yeast extract demonstrated a dose-dependent improvement in dermal collagen density and inhibition of enzymes such as collagenase and elastase, while increasing antioxidant enzyme activities such as SOD and GPx. To the best of our knowledge, this is the first study to assess the multifaceted impact of yeast extract across diverse aspects of skin aging using both cellular models and a photoaging-induced hairless mouse model.

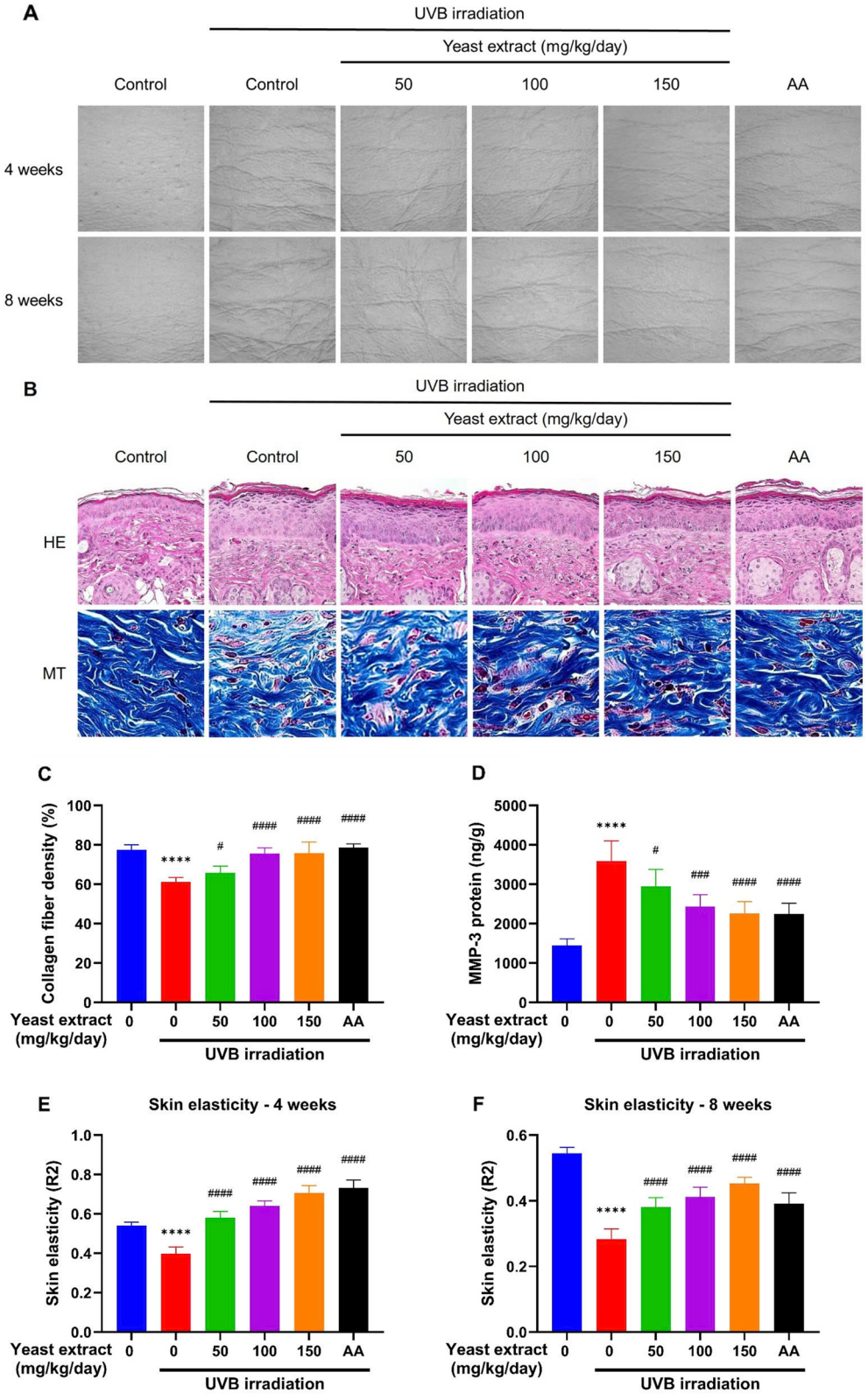

Fig. 6 (See legend on next page.)

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Fig. 6 Anti-wrinkle properties of yeast extract intake in the photoaging-induced mouse model. **A**, Images of mouse skin surface after 4 and 8 weeks. **B**, HE and MT staining of mouse skin tissues. UVB irradiation caused a decrease in collagen fiber density (**C**) and upregulated MMP-3 protein levels (**D**) after 8 weeks, but the yeast extract diet significantly reversed these changes. Regarding skin elasticity, UVB exposure decreased R2 values after 4 (**E**) and 8 weeks (**F**), and oral administration of yeast extract improved it. HE, Hematoxylin and Eosin; MT, Masson's trichrome; AA, Ascorbic acid, 100 mg/kg/day; MMP, matrix metalloproteinase; UVB, ultraviolet B. $^{****}p < 0.001$ by independent samples t-test compared to non-irradiated control group; $^{\#}p < 0.05$, $^{\#\#\#}p < 0.005$, $^{\#\#\#\#}p < 0.001$, independent samples t-test compared to UVB-irradiated control group

Our study highlighted significant improvements in skin hydration following treatment with *S. cerevisiae* yeast extract. The yeast extract increased HA levels and upregulated HAS-2 expression while inhibiting hyaluronidase-1 HYAL-1, suggesting a robust mechanism for maintaining and enhancing skin moisture. HA, a key glycosaminoglycan in the epidermis and extracellular matrix, is critical for retaining water molecules, ensuring hydration and elasticity of the skin [17]. HAS-2, one of HAS isoforms, promotes HA synthesis, whereas HYAL-1, one of HYAL isoforms, catalyzes its degradation [17]. In extrinsic aging, UVB radiation causes the downregulation of HAS and the upregulation of HYALs, leading to a decrease in HA production in histopathological studies [18–20]. By modulating these pathways, yeast extract supports the structural integrity and hydration of the skin. The findings align with other studies showing the efficacy of HA-related treatments. In randomized controlled trials, oral hyaluronan supplementation has been reported to significantly enhance skin hydration, reduce TEWL, and improve skin elasticity [21, 22]. Similarly, yeast extract-based formulations have been shown to bolster skin hydration and enhance epidermal moisture retention through their bioactive compounds [9]. Compared to other antioxidants like vitamins C and E, yeast extract offers a unique advantage due to its direct impact on HA metabolism and additional antioxidant effects similar to botanical extracts, such as *Cannabis sativa* or *Allium pseudojaponicum* [1, 23]. This dual action underscores its potential as a comprehensive anti-aging and hydrating agent.

This study demonstrated that yeast extract significantly mitigated the molecular mechanisms underlying skin wrinkle formation, improving collagen and elastin integrity while reducing the activity of MMPs such as MMP-1, MMP-3, and MMP-9. It also suppressed collagenase and elastase activity, both of which contribute to extracellular matrix degradation, loss of elasticity, and the formation of wrinkles [24]. Furthermore, yeast extract reduced epidermal thickening induced by UVB irradiation, which often accompanies photoaging [25]. Mechanistically, photoaging disrupts the balance between collagen production and degradation, leading to reduced collagen levels and increased breakdown by enzymes like MMPs [24]. Elastin, another crucial protein for skin elasticity, is similarly degraded by elastase [24]. Histopathological evidence has confirmed these findings via fragmentation and lower amounts of collagen and elastin in aged dermis [26, 27]. By inhibiting MMPs and elastase, yeast extract helps preserve the structural components of the dermal extracellular matrix, which supports skin tightness and resilience. Comparatively, oral collagen peptides and antioxidants have shown similar efficacy in clinical settings. For example, low-molecular-weight collagen peptides significantly reduced wrinkle depth, improved skin hydration, and elasticity in clinical trials [28]. Additionally, plant-based antioxidants, such as cacao powder, inhibit MMP activities and stimulate collagen synthesis [29]. These findings corroborate the role of bioactive compounds in promoting skin health by targeting molecular pathways related to aging. All in all, while yeast extract demonstrates broad efficacy in reducing wrinkle formation and improving elasticity through multiple mechanisms, its combination with established oral rejuvenating agents like collagen peptides could offer synergistic benefits. This integrated approach could enhance anti-aging regimens and address diverse aspects of skin health.

Our study revealed the strong antioxidant properties of *S. cerevisiae* yeast extract, showing significant upregulation of key antioxidant enzymes such as SOD and GPx. SOD catalyzes the conversion of superoxide radicals to hydrogen peroxide, while GPx reduces hydrogen peroxide to water using glutathione as a substrate [30]. Glutathione itself, a major non-enzymatic antioxidant, plays a vital role in maintaining cellular redox balance [31]. Oxidative stress occurs when the production of ROS due to aging and UV exposure surpasses the neutralizing capacity of the antioxidant defense system, leading to molecular damage in proteins, lipids, and DNA [30]. By mitigating oxidative stress, yeast extract helps protect dermal cells from ROS-induced damage, which otherwise accelerates skin aging. Similar findings have been reported in other studies. To illustrate, research on high-glutathione-producing strains of *S. cerevisiae* demonstrated a significant enhancement in intracellular glutathione levels, emphasizing yeast's ability to act as an antioxidant reservoir [32]. These strains also support cellular redox balance, reducing oxidative damage to proteins, lipids, and DNA. Another study on spent brewer's yeast showed its potential as a functional ingredient, with bioactive peptides that exhibit antioxidant properties, further affirming yeast's ability to mitigate oxidative stress [33]. Additionally, oral rejuvenating agents such as vitamin C, hesperidin, cacao powder, and other

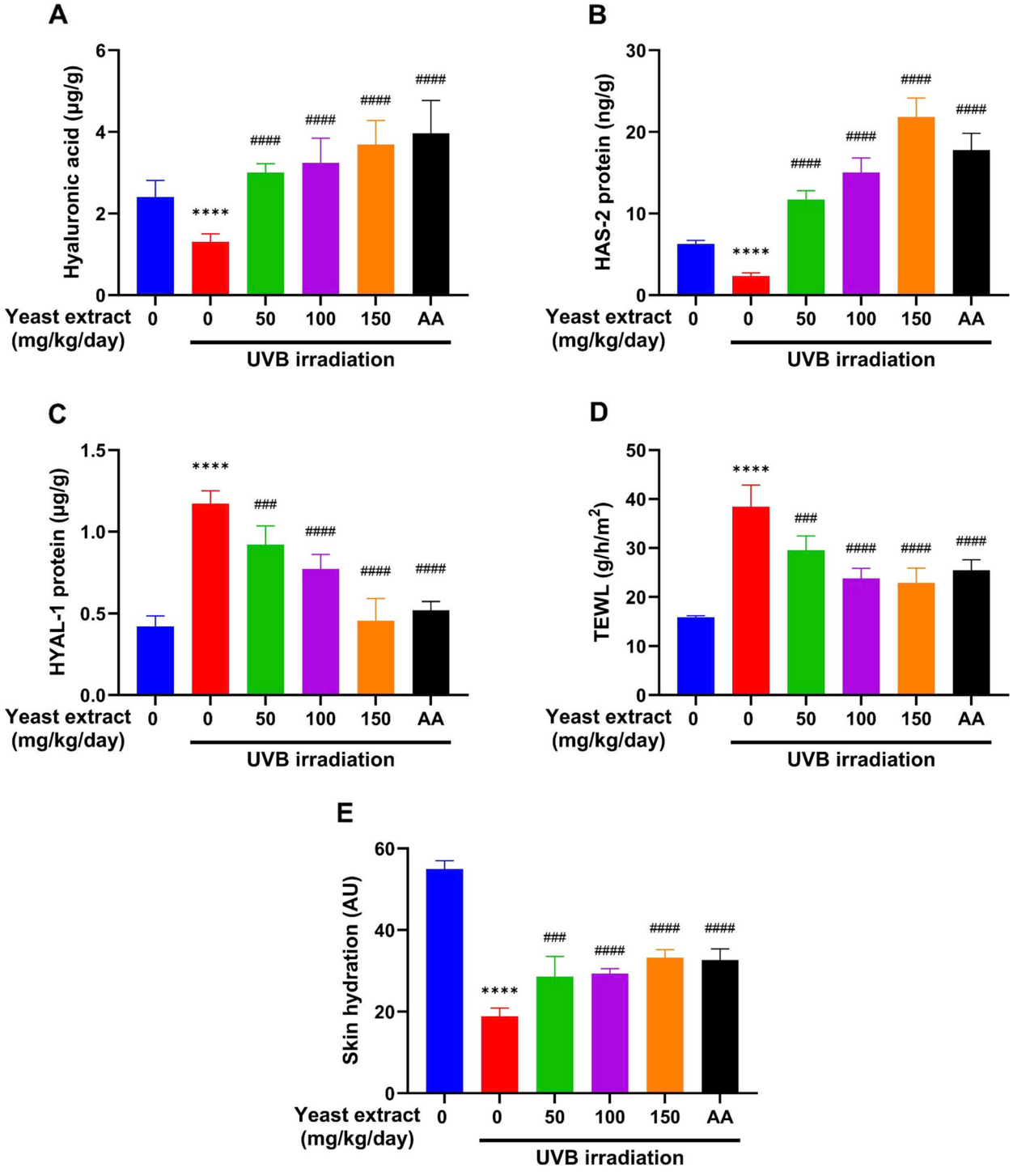

Fig. 7 Skin moisture improvement in the photoaging-induced mouse model after yeast extract consumption. UVB irradiation reduced hyaluronic acid (**A**), and HAS-2 (**B**), while increasing HYAL-1 (**C**), TEWL (**D**), ultimately lessening skin hydration (**E**). Oral administration of yeast extract significantly reversed these effects, leading to an improvement in skin hydration. HAS-2, hyaluronic acid synthase-2; HYAL-1, hyaluronidase-1; TEWL, trans-epidermal water loss; UVB, ultraviolet B. $^{****}p < 0.001$, independent samples t-test compared to non-irradiated control group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.005$, $^{\#\#\#\#}p < 0.001$, independent samples t-test compared to UVB-irradiated control group

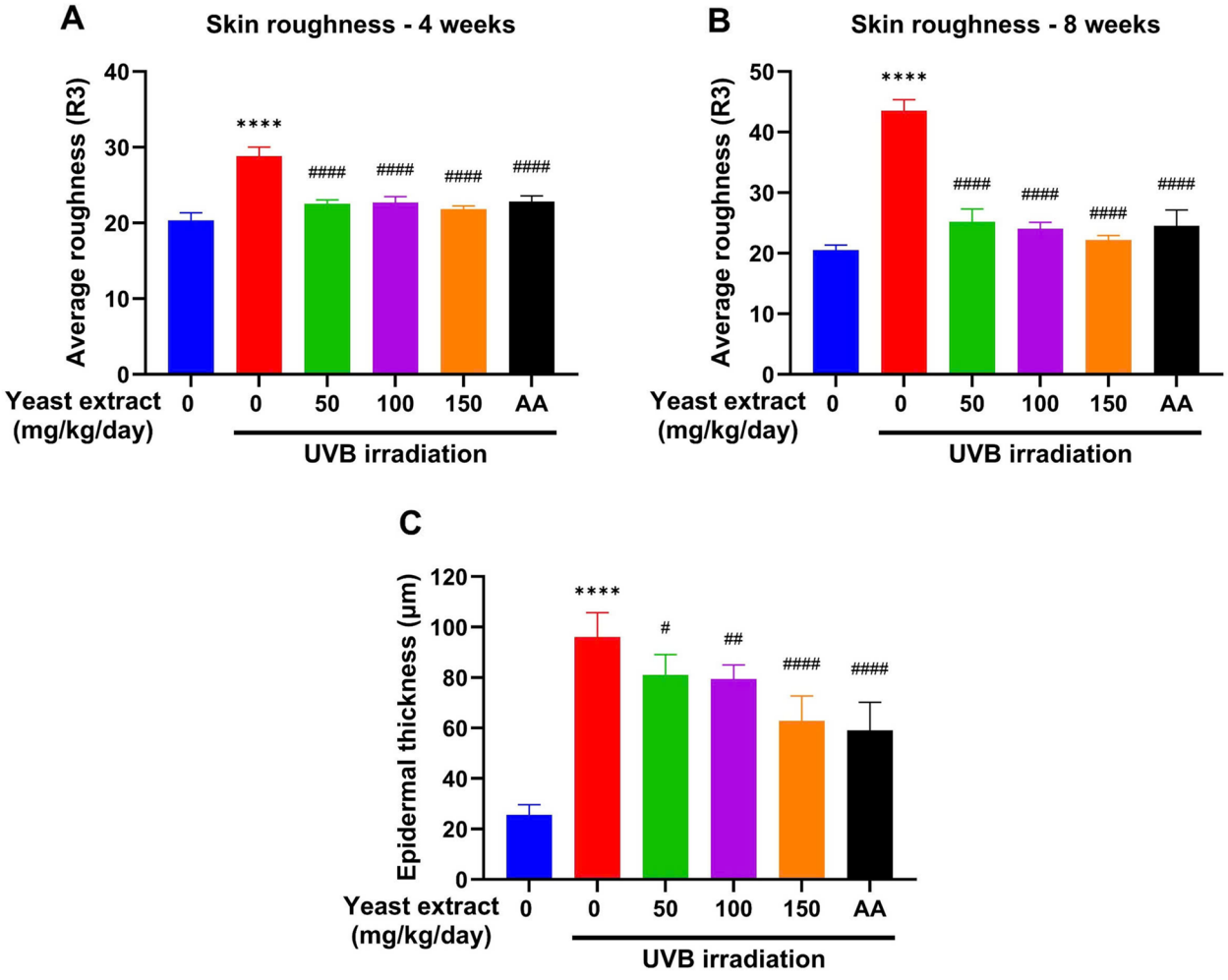

Fig. 8 Improvement in skin roughness and thickness in the photoaging-induced mouse model after yeast extract consumption. Yeast extract significantly reduced skin roughness caused by UVB irradiation after 4 weeks (**A**) and 8 weeks (**B**). The oral consumption of yeast extract also decreased UVB-induced epidermal thickness after 8 weeks (**C**). UVB, ultraviolet B. $^{****}p < 0.001$, independent samples t-test compared to the non-irradiated control group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#\#}p < 0.001$, independent samples t-test compared to the UVB-irradiated control group

flavonoids have shown similar benefits by inhibiting oxidative damage and supporting collagen integrity in aging skin [29, 34]. These findings align with the broader literature emphasizing the role of antioxidants in combating aging. Yeast extract's unique combination of bioactive antioxidants offers a potent defense against oxidative stress, making it a promising candidate for inclusion in anti-aging regimens. Compared to single-compound antioxidants, the complex antioxidant profile of yeast extract may provide synergistic benefits, reinforcing its therapeutic potential.

This study displayed the anti-inflammatory effects of yeast extract, showing its ability to downregulate key inflammatory mediators such as IL-1β, IL-6, TNF-α, and COX-2. These molecules are central to the process of inflammaging, a chronic, low-grade inflammatory state associated with aging [35]. TNF-α, IL-1β, and IL-6 are pro-inflammatory cytokines that promote immune cell recruitment and activation, leading to tissue damage and impaired skin regeneration [35]. COX-2, an enzyme induced by these cytokines, drives the production of prostaglandins that exacerbate inflammation [36]. Yeast extract effectively mitigates these pathways, enhancing skin health by downregulating inflammatory mediators. Similar findings have been reported in other studies. For instance, research on selenium-enriched yeast showed reduced expression of IL-1β and TNF-α in inflammatory conditions, highlighting yeast's capacity to modulate cytokine profiles and restore tissue homeostasis [37]. Additionally, spent brewer's yeast has demonstrated bioactive properties, with peptides reducing systemic inflammation and oxidative damage [33]. Collectively, these findings underscore the therapeutic potential of yeast-based interventions for skin rejuvenation and inflammation control.

The strengths of our study lie in its comprehensive approach to evaluating the anti-aging and anti-inflammatory effects of *S. cerevisiae* yeast extract. By utilizing both in vitro and in vivo models, the study provides a robust dataset that demonstrates the extract's potential to improve skin hydration, reduce oxidative stress, and mitigate inflammatory markers. Additionally, the study explores multiple endpoints of skin aging, including elasticity and wrinkle formation, thus providing a holistic view of the extract's benefits. However, our study also has some limitations. First, while the laboratory results are promising, the clinical relevance of the findings could be further validated with human trials to ensure safety, efficacy, and optimal dosage in diverse populations. Furthermore, the study mainly focused on short-term effects, leaving questions about the long-term sustainability of yeast extract's benefits for skin health. Additionally, although the study attributed the observed effects to the antioxidant and anti-inflammatory properties of yeast, it did not identify all the specific bioactive compounds responsible, which could be important for further targeted applications. Future studies should address these gaps by exploring the specific active components of yeast extract and evaluating its long-term clinical benefits.

Conclusion

In conclusion, this study demonstrates the significant potential of *S. cerevisiae* yeast extract as a multifunctional anti-aging agent. The yeast extract showed promising results in improving skin hydration, reducing wrinkles and oxidative stress, as well as mitigating inflammation by downregulating key inflammatory markers. These findings provide a strong foundation for its use in skincare, offering a natural alternative for addressing the molecular drivers of skin aging, including oxidative damage and inflammaging.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12866-025-04593-1.

Additional file 1: Figure S1. Cell viability of HDF and KC based on different concentrations of yeast extract and UVB irradiation. UVB, ultraviolet B; HDF, human dermal fibroblast; KC, keratinocyte. *$p < 0.05$, **$p < 0.01$, ****$p < 0.001$, independent samples t-test compared to UVB-irradiated control group. The error bars are based on standard deviation.

Additional file 2: Figure S2. Body weight measurement of mouse groups at one-week intervals after 8 weeks. UVB, ultraviolet B; AA, ascorbic acid.

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Clinical trial number
Not applicable.

Authors' contributions
N.H.N., Y.I.L., Y.S.J., H.K.L., I.J., and S.J.L. performed the experiments. N.H.N. and Y.I.L. designed the research study. Y.S.J., H.K.L., I.J., and S.J.L. contributed essential resources. N.H.N. and Y.I.L. validated the data. N.H.N., Y.I.L., Y.S.J., H.K.L., I.J., and S.J.L. analyzed the data. N.H.N. and Y.I.L. wrote the original draft of the paper. Y.I.L. and J.H.L. reviewed and edited the manuscript. N.H.N. and Y.I.L. prepared the visualizations. J.H.L. supervised and administered the project. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Experimental procedures were approved by the Institutional Animal Care and Use Committee (Approval number: Hulux-2024–06-001) and conducted in compliance with ethical guidelines (the AVMA Guidelines for the Euthanasia of Animals (2020 edition)).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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