IFSCC 2025 full paper (IFSCC2025-484)

# *"Fermented Galla rhois gallnut extract alleviates photoaging by reducing oxidative stress and enhancing mitochondrial function in UV-damaged cells"*

**Jiaying Wu[1], Xiang Li[1], Denghui Chen[1], Xin Yan[1],Yi Zhang[1], Guang Yang[1], Hu Huang[1*]**

[1] Proya International Academy of Sciences, Proya Cosmetics Co., Ltd, Hangzhou, China

## 1. Introduction

Skin aging represents a multifaceted biological phenomenon, clinically manifested by wrinkle formation, loss of dermal elasticity, tissue laxity, pore enlargement, and irregular pigmentation patterns [1]. In addition to natural aging caused by irresistible factors in the body, exogenous skin aging, also known as photoaging, which is exposure to ultraviolet (UV) radiation, accelerate the aging process [2]. Some researches suggest UV radiation-induced cutaneous aging may center on mitochondrial-mediated mechanisms, particularly through reactive oxygen species (ROS) generation and impaired electron transport chain function [3,4]. The increase of oxidative stress and insufficient energy metabolism in skin cells further aggravate the skin aging[4]. Therefore, improving cellular mitochondrial function is considered as a good method to protect and alleviate skin photoaging.

*Galla rhois*, a traditional Chinese medicinal material, refers to the gall formations induced by the Chinese aphid Schlechtendalia chinensis (Bell) on Rhus chinensis leaves [5]. Some studies have demonstrated that *Galla rhois* possesses anti-inflammatory, hemostatic, and analgesic properties, with therapeutic applications including promoting post-traumatic coagulation, burn treatment, and antimicrobial skin therapies [6]. In addition, Yang et al. reported that among 30 analyzed Chinese vegetables and medicinal plants, *Galla rhois* exhibits the most potent antioxidant activity, attributed to its high concentrations of tannins, ellagic acid, and Gallic acid derivatives [7]. These polyphenols have been reported to improve mitochondrial function, alongside their well-documented antioxidant effects [8]. Thus, *Galla rhois* extract demonstrates therapeutic potential for enhancing mitochondrial function through its bioactive components. Fermentation converts complex organic substrates into simpler compounds through microbial activity, while generating activity-rich metabolites [9]. Fermentative microorganisms encompass a wide range of species, among which lactic acid bacteria (LAB) are the most prevalent. In vitro and animal studies confirm that fermented plant extracts by LAB exhibit improved anti-inflammatory, antimicrobial, and immunomodulatory activities compared to non-fermented counterparts [10]. Therefore, it is a good way to enhance the bioactivity of *Galla rhois* by LAB fermentation.

In this study, we developed a kind of novel fermented ingredient fermentated *Galla rhois* gallnut extract (FGRE) by *Lactiplantibacillus plantarum* and explored the effect on protecting photoaging. FGRE were explored the effect on DPPH radical scavenging activity and elastase

inhibitory activity by biochemical experiments. The ROS inhibition was determined in UV-damaged human keratinocytes (HaCaT) cells with FGRE intervention. The Oxygen Consumption Rate (OCR) of mitochondrial respiratory metabolism, ATP concentration and $NAD^+$/NADH were analyzed in UV-induced human dermal fibroblasts (HDF) cells. In addition, the transcription levels of mitochondrial function-related genes were also assessed. Our results indicated that FGRE could reduce oxidative stress and improve the mitochondrial function, which provided a novel photoprotection ingredient for skin care.

## 2. Materials and Methods

### *2.1. Chemicals and Reagents*

GRE was purchased from Focusherb Co. Ltd (Shanxi, China). *Lactiplantibacillus plantarum* PIAS240228 was isolated from fermented food by our laboratory. Fermented nutrient salt NS01 was obtained from AngelYeast Co., Ltd. HDF cells purchased from Guangdong BioCell Biotech Co., Ltd (Guangdong, China). HaCaT cells were obtained from Meisen Cell technology Co., Ltd (Zhejiang, China). All other chemicals of analytical grade were obtained from Sigma (Shanghai, China), unless otherwise noted.

### *2.2. Biochemical Experiments*

The antioxidant activity of FGRE was determined by DPPH radical scavenging assay according to the method described by Lee et al [11]. Briefly, the samples were mixed with an equal amount of DPPH solution and and left to stand for 30 min at room temperature in the dark. And then determine the absorbance of the resulting solution at 517 nm. Water was taken as control, while 12.5 μg/mL ascorbic acid (Vc) was taken as positive control. The scavenging ability was defined as: Scavenging activity (%) = $(A_{control}-A_{sample})/A_{control} \times 100\%$.

The anti-elastase activity was measured according to Shirzad's research with slight modification [12]. 420 μl 0.05 M Tris-HCl (pH = 8), 180 μl of samples and 150 μl elastase enzyme (600 mU/ml) were mixed together with 15 min incubation in room temperature (25 °C). 150 μl N-succinyl-Ala-Ala-Ala-Val-p-nitroanilide substrate (1.015 mmol/L) was added to each tube. After 20 min incubation in room temperature (25 °C), absorbance was read at 410 nm. The epigallocatechin gallate (EGCG, 500 μg/mL) was used as positive control. The percentage inhibition was calculated as follows: Inhibition (%) = $[(A_{control}-A_{sample})/A_{control}] \times 100\%$.

### *2.3. Cell Cytotoxicity Assay*

The effects of FGRE on HaCaT and HDF cell viability were determined using a Cell Counting kit-8 (CCK-8) assay [13]. Briefly, activated cells were treated with different concentrations of FGRE for 24 h (37°C, 5% $CO_2$). Then, cells were incubated with CCK-8 reagent for 2 h and determined the absorbance at 450 nm. The calculation of relative cell viability: relative cell viability (%) = $[(A_{sample}-A_{blank}) / (A_{control}-A_{blank})] \times 100\%$.

### *2.4. ROS Content Analysis*

The pre-activated HaCaT cells in both control and model groups were cultured in DMEM medium for 24 h, while the sample group received 1% FGRE treatment for 24 h. After that, the cells in model and FGRE groups were irradiated with UVB (210 mJ/$cm^2$). Intracellular ROS levels were detected using 2',7'-dichlorofluorescin diacetate (DCFH-DA) fluorescent probe. Fluorescence intensity of DCFH-DA was measured at excitation/emission wavelengths of 488 nm and 525 nm respectively using a fluorescence microplate reader. Cellular ROS levels

across experimental groups were expressed as fluorescence intensity values. The relative ROS content was calculated as follow: ROS content (%) = $A_{sample}/A_{model}$ × 100%.

### *2.5. Mitochondrial Respiratory Metabolism Assessment*

The HDF cells were used to explore the effect of FGRE on mitochondrial. The cells in FGRE group were cultured in 1% FGRE for 24 h, while cells in other groups with normal culture. After UVB-induced modeling (180 mJ/cm$^2$), the OCR in HDF cells was determined by Seahorse Extracellular Flux (XF) analyzer (Seahorse Bioscience, USA) , and analyzed the basal respiration, ATP production, maximal respiration and spare respiratory capacity according to Gu's research [14].

### *2.6. ATP Content and NAD$^+$/NADH Determination*

The HDF cells in FGRE group were treated with 1% FGRE for 24 h, while cells in control and model groups with no-treatment. Then, FGRE and model group were modeled with UVA irradiation (30 J/cm$^2$). The cells were washed 2~3 times with phosphate buffer and collected for detection of ATP content and NAD$^+$/NADH. The ATP content and NAD$^+$/NADH were analyzed by using commercial assay kits (Beyotime, Shanghai, China) according to the instructions of the manufacturer.

### *2.7. Quantitative Real-Time Polymerase Chain Reaction (qRT-PCR) Assay*

The HDF cells were pre-treated and modeled as described as 2.6, and collected cells for RNA extraction. Total RNA was extracted from the HDF cells using a commercial kit (Takara, Japan) following the protocol of the manufacturer. Complementary DNA (cDNA) was synthesized using a commercial kit (Accurate Biology Co., Ltd., Hunan, China). The mRNA transcription levels of MFN1(Mitofusin 1), OPA1(Optic Atrophy 1), DRP1 (Dynamin-related protein 1) and FIS1 (Fission 1) were estimated using a qRT-PCR system (Roche, Basal, Swiss). The gene sequences of the primers were obtained from the references and listed in Table 1.

**Table 1.** Gene Sequences of Primers

| Genes | Forward primer (5′−3′) | Reverse primer (5′−3′) |
|---|---|---|
| MFN1 | CACAGGGGATGCCAGAAAGT | TTCACTGCTGACTGCGAGAT |
| OPA1 | ATCATCTGCCACGGGTTGTT | ATAGGGCCACATGGTGAGGA |
| DRP1 | AGTGGTGACTTGTCTTCTTCGTAA | TAGCCTGTTTCTCCTTTGTTCCT |
| FIS1 | CCAAGAGCACGCAGTTTGAG | GACGTAATCCCGCTGTTCCT |

### *2.8. Statistical Analysis*

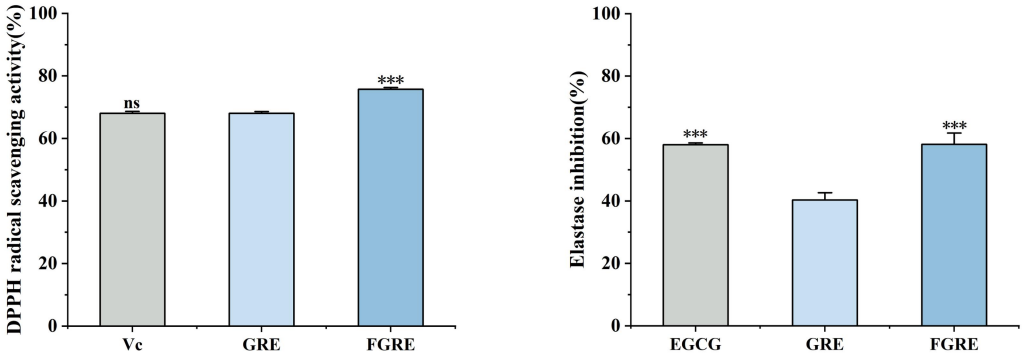
The data were analyzed using one-way analysis of variance (ANOVA) with SPSS 22.0 and Origin 9.0 software. Results are presented as the mean ± standard error of the mean (SEM). The Tukey's post hoc test was applied following one-way ANOVA to determine statistically significant differences among different groups : *, $p$<0.05; **, $p$<0.01; ***, $p$<0.001.

## 3. Results

### *3.1. Antioxidant Activity and Anti-elastase Activity of FGRE*

The biochemical experimentes were used to explore the effect of FGRE on antioxidant and anti-elastase activity (Figure 1). The results demonstrated DPPH radical scavenging activity of 75.74% and elastase inhibition of 58.12% for FGRE. Notably, FGRE exhibited significantly stronger antioxidant and anti-elastase effects compared to GRE ($p$<0.001), suggesting that

fermentation enhances the bioactivity of GRE. Thus, the further effect of FGRE was explored by cellular experiments.

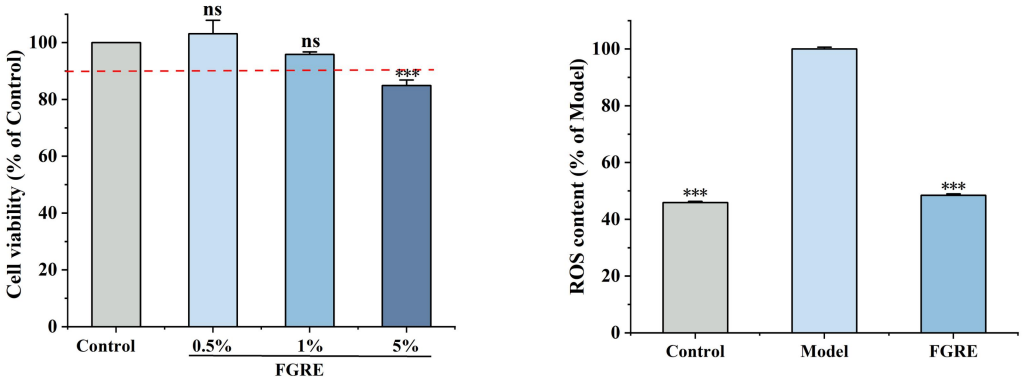



(**a**) (**b**)

**Figure 1.** The bioactivity of FGRE determined by biochemical experiments. (a) DPPH radical scavenging assay; (b) Anti-elastase activity.

### *3.2. ROS Inhibition of FGRE in HaCaT Cells*

The ROS content was determined to assess the antioxidant activity of FGRE in UV-induced HaCaT cells. As shown in Figure 2, FGRE concentrations below 1% showed no statistically significant impact on cell viability ($p$>0.05), leading to the selection of 1% FGRE as the experimental concentration. The level of ROS in model group was obviously higher than that in control group ($p$<0.001), suggesting that UV irradiation caused cellular oxidative stress. Differently, 1% FGRE treatment markedly reduced the ROS content with the inhibition rate of 52.41% compared to model group ($p$<0.001). The results indicated that FGRE could effectively attenuated the ROS generation induced by photoaging.




(**a**) (**b**)

**Figure 2.** The effect of FGRE on inhibiting ROS generation in HaCaT cells. (a) Cell viability; (b) ROS content.

### *3.3. Mitochondrial Respiratory Enhancement of FGRE in HDF Cells*

The results of CCK-8 showed that different concentration (1%~10%) of FGRE was no harmful to HDF cells survival (Figure 3a). Considering the previous experimental results, 1% FGRE was was determined as the experimental concentration to investigate the effects on mitochondrial respiration in HDF cells. Compared with the control group, the OCR levels of basal respiration, ATP production, and maximal respiration in the model group showed significant decreases ($p$<0.001), indicating UV-induced mitochondrial dysfunction (Figure 3). 1% FGRE intervention effectively ameliorated mitochondrial impairment in UV-induced HDF

cells, as evidenced by obvious upregulation of ATP production, basal respiration, maximal respiration and spare respiratory capacity ($p$<0.001). These results suggested that FGRE could enhance cellular mitochondrial respiratory to protect the damage induced by UV.

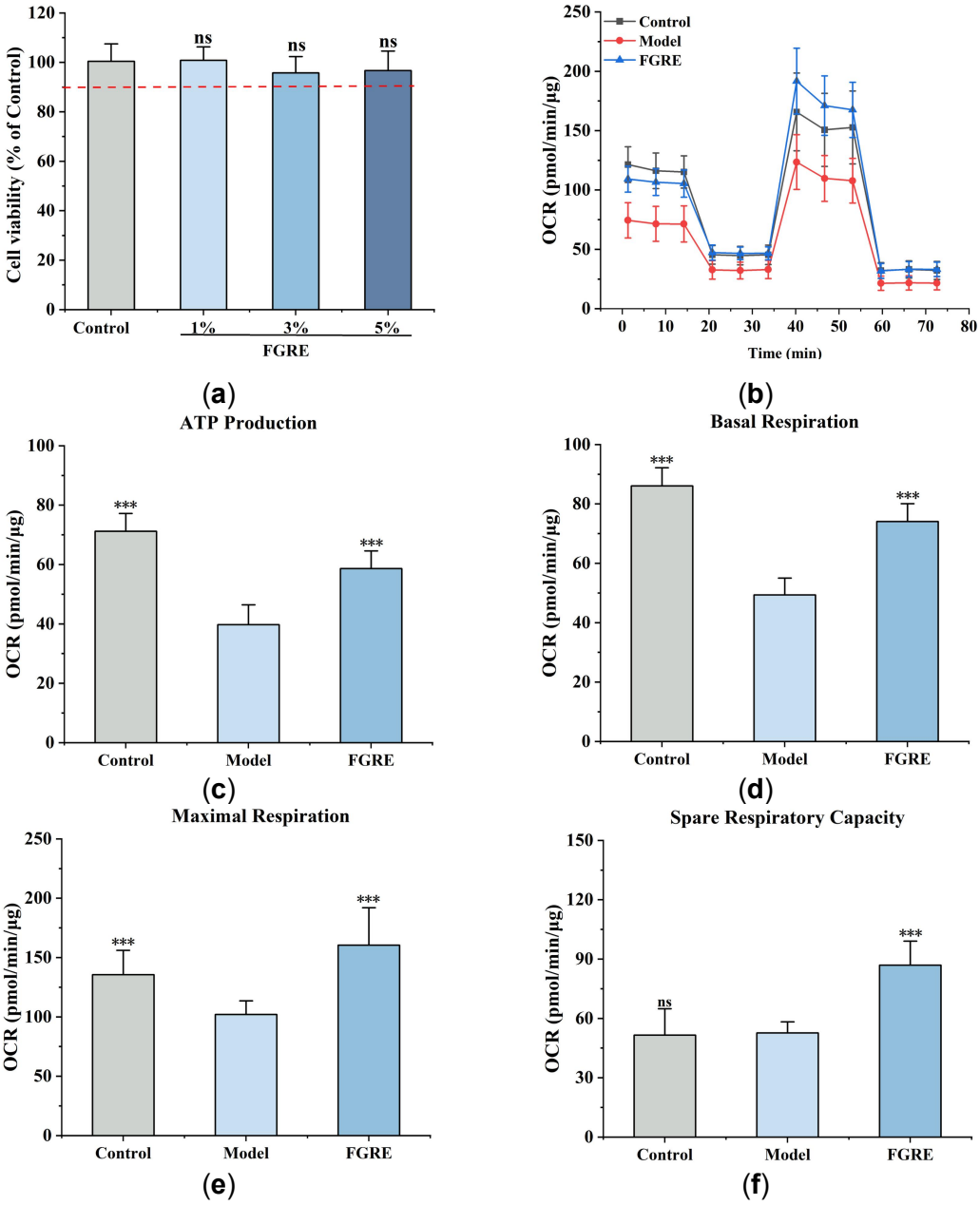



**Figure 3.** The effect of FGRE on cellular mitochondrial respiratory function. (a) Cell viability; (b) Cellular OCR curve; (c) ATP production; (d) Basal respiration; (e) Maximal respiration; (f) Spare respiration capacity.

### *3.4. ATP Content and NAD⁺/NADH Upregulation of FGRE in HDF Cells*

To assess the effect of FGRE on mitochondrial energy metabolism, the ATP content and NAD⁺/NADH were determined in UV-induced HDF cells (Figure 4). Compared with control group, UV irradiation caused a sharp decline of ATP content and NAD⁺/NADH ratio in model group ($p$<0.001). FGRE not only significantly increased ATP generation in UV-damaged HDF cells($p$<0.001), but also apparently upregulated the ratio of NAD⁺/NADH ($p$<0.01). Thus, FGRE improved cellular mitochondrial energy metabolism as well.

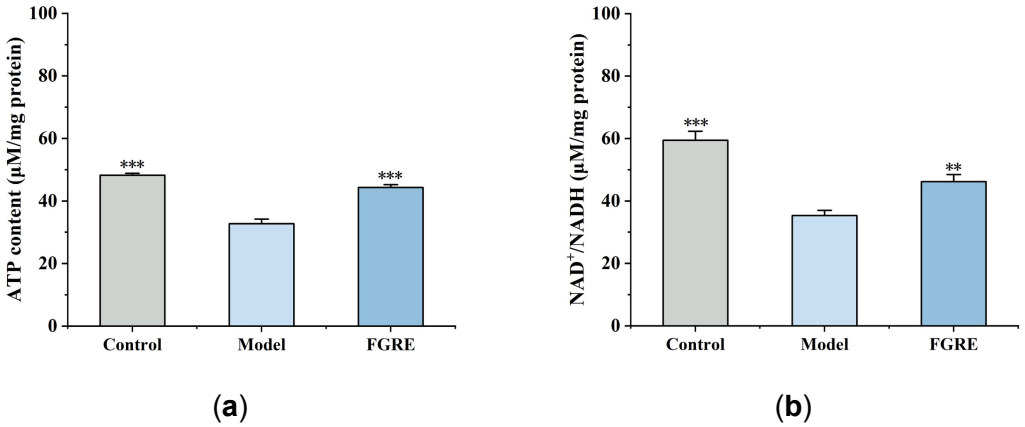



**Figure 4.** The effect of FGRE on cellular mitochondrial energy metabolism. (a) ATP content; (b) $NAD^+$/NADH.

### *3.5. Mitochondrial Fusion and Fission of FGRE in HDF Cells*

To further explore the effect of FGRE, the transcription levels of mitochondrial fusion and fission genes were analyzed. The transcription levels of fusion genes MFN1 and OPA1 in model group were obviously lower than that in control group, while the levels of fission genes DRP1 and FIFS1 were significantly higher ($p$<0.001) (Figure 5). Differently, FGRE intervention evidently improved the relative mRNA expression of MNF1 and OPA1, and markedly declined the transcription levels of DRP1 and FIS1 ($p$<0.001). The data indicated that FGRE facilitated mitochondrial homeostasis recovery in UV-induced damaged HDF cells, restoring their functional state toward normal cellular levels.

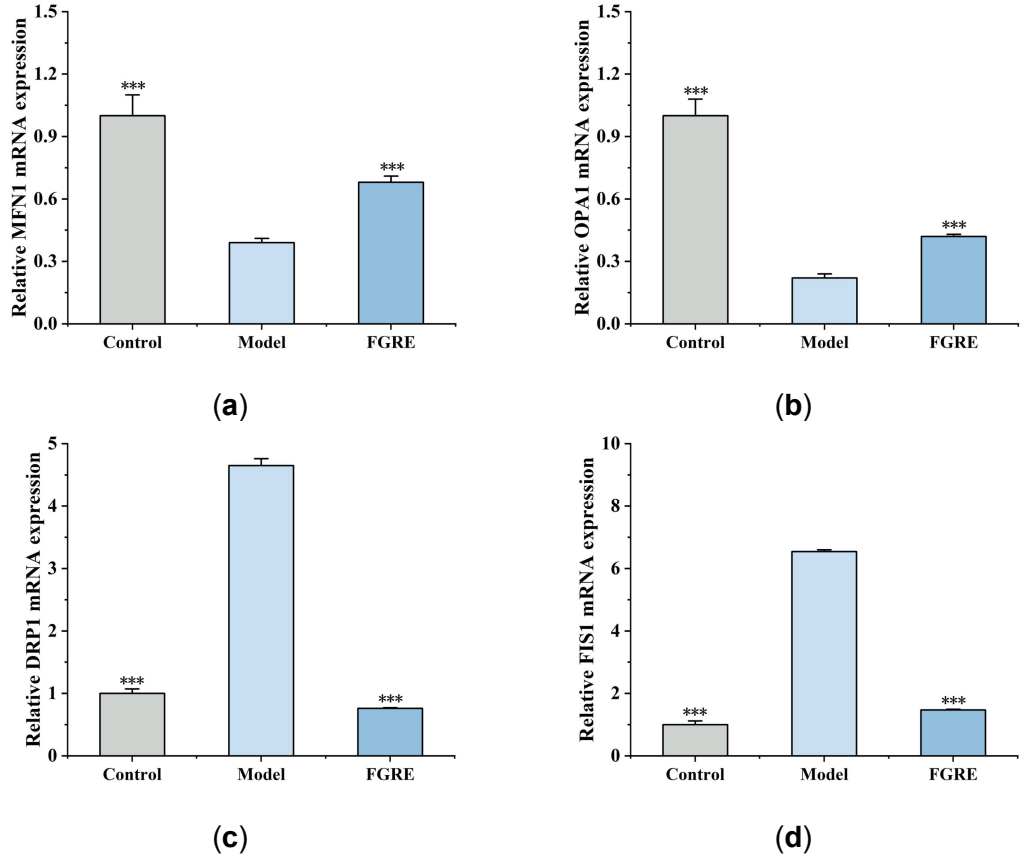


**Figure 5.** The effect of FGRE on relative mRNA expression of mitochondrial fusion and fission genes. (a) MFN1; (b) OPA1; (c) DRP1; (d) FIS1.

## 4. Discussion

*Galla rhios* is serving as an orally administered agent in traditional Chinese medicine formulations, while also used topically in clinical settings for burn wound care and tissue regeneration.

We used microbial fermentation technology to obtain FGRE by using *Lactiplantibacillus plantarum*. The results showed that FGRE had significantly higher antioxidant and anti-elatase activity than unfermented extract. In addition, FGRE inhibited the ROS generation and enhanced the mitochondrial function in UV-damaged cells.

*Galla rhios* extract have been reported to promote wound healing by reducing oxidant stress and enhancing the expression of Type I and III collagen in HaCaT cells and dermal fibroblasts, may due to the high content of tannins and flavonoids [15]. Fermentation is one of the most conventional but still prevalent bioprocessing methods in the food or material industry, with the potential to increase polyphenol and flavonoid content and enhance its nutritive value [16]. Therefore, the enhanced bioactivity of FGRE can be attributed to metabolite alterations induced during fermentation processes. The bioactive compounds may derive from metabolites produced by *Lactiplantibacillus plantarum* own. For example, Lipoteichoic acid derived from *Lactiplantibacillus plantarum* demonstrated anti-photoaging activity in human skin cells through downregulation of matrix metalloproteinase-1 expression [17]. On the other hand, tannins and flavonoids were transformed into more active small molecules. Some research suggested tannins especially ellagitannins could be converted into urolithin A and its derivatives by *Lactiplantibacillus plantarum*, which had anti-inflammatory, antioxidant, antimelanogenic and anti-aging effects on the skin [18]. Since *Galla rhios* extract contains tannins and flavonoids, the Urolithin A and other bioactive metabolites are possibly present in FGRE.

ROS are are the molecules containing highly unstable oxygen radicals, including superoxide ($O_2$•−), hydrogen peroxide ($H_2O_2$), the hydroxyl radical (•OH), and singlet oxygen ($^1O_2$) [19]. And ROS accumulation in skin is a direct marker of oxidative stress, while oxidative stress is a crucial factor that affects skin cellular senescence [20]. Long-term exposure to UV radiation, which is the primary cause of extrinsic photoaging, stimuli trigger ROS production in the skin, further reducing antioxidant levels in the skin and damaging DNA, proteins, and lipids [21]. Thus, inhibiting the generation of ROS and reducing the oxidative stress are the key to ameliorate and protect photoaging. In our study, we confirmed the antioxidant activity of FGRE by DPPH radical scavenging assay and ROS inhibition analysis in UV-induced HaCaT cells. Actually, oxidative stress exhibits a strong mechanistic association with mitochondrial metabolism and functional integrity. ROS are produced mainly through cellular oxidative metabolism during ATP generation from glucose and mitochondrial dysfunction in aging [22]. Under normal conditions, ROS generation and scavenging maintain a delicate dynamic balance in mitochondria. Excessive production and insufficient scavenging of ROS will induce mitochondrial damage and impair their normal physiological functions. Mitochondrial impairment exacerbates ROS production and accumulation, thereby establishing a self-reinforcing cycle that accelerates cutaneous aging [23]. Thus, to develop a kind of novel ingredient, its effects on mitochondrial functional integrity necessitate evaluation.

To assess the effect of FGRE on mitochondrial function, the Seahorse XF analyzer was used to dynamically monitor cellular energetics in UV-irradiated HDFs. The experiments analyzed the OCR of basal respiration, ATP production, maximal respiration and spare respiratory capacity, serving as biomarkers of cellular metabolic adaptability to energy demand

fluctuations. A few research suggested that the OCR decline of basal respiration and ATP production was a consequence of a reduced activity or malfunction of the mitochondrial respiratory chain [24]. In our study, the OCR levels of basal respiration and ATP production in UV-induced cells were significantly lower than that in normal cells, indicated that UV irradiation damaged cellular mitochondria. Differently, FGRE intervention attenuated UV-induced damage to mitochondrial respiratory function, while concurrently enhancing ATP synthesis capacity and restoring $NAD^+$/NADH redox homeostasis. NAD is a kind of co-factor (or co-enzyme) in oxidation-reduction reactions, with two distinct redox states: reduced (NADH) and oxidized ($NAD^+$) forms [25]. Because mitochondria oxidize NADH to $NAD^+$ , mitochondrial dysfunction can decrease the $NAD^+$/NADH ratio [26]. In addition, ATP generated is also critical for $NAD^+$ regeneration from NADH. Uncoupling respiration from ATP synthesis or increasing ATP hydrolysis restores $NAD^+$/NADH homeostasis and proliferation even under elevated glucose oxidation [26]. Therefore, elevated ATP synthesis coupled with an enhanced $NAD^+$/NADH ratio synergistically improve mitochondrial bioenergetics and promote UV-induced damage repair.

Mitochondria constantly undergo fission and fusion, known as 'mitochondrial dynamics', is aimed to adapt to alterations in the cellular environment and keep the homeostasis of mitochondria structure and function. Mitochondrial fusion occurs in two steps : MFN1/2-mediated outer membrane fusion regulated, and OPA1-dependent inner membrane fusion coordinated [27]. When cellular ATP demand increases, enhanced mitochondrial fusion merges individual organelles to stabilize the internal environment, thereby improving energy production efficiency. Meanwhile, fusion expands the mitochondrial matrix volume to facilitate metabolite exchange and optimize energy utilization [28]. DRP1 and FIS1 are involved in the regulation of mitochondrial fission. Mitochondrial fission leads to morphological fragmentation and is associated with mitochondrial uncoupling and permits segregation of dysfunctional mitochondria to become targets of mitochondrial autophagy [29]. The effect of mitochondrial fission and fusion imbalance on aging is unquestionable and exerts an important role in the skin aging process. Current research has not yet established the role of mitochondrial fusion genes (MFN1/OPA1) in cutaneous aging [30]. However, some studies suggested that inhibiting the expression of Drp1 in skin cells may delay aging [31]. According to our results, FGRE promoted the expression of fission genes and inhibited the fusion genes expression in UV-damaged cells, indicating that FGRE potentially prevent the photoaging by regulating the mitochondrial kinetic homeostasis.

## 5. Conclusion

During photoaging, skin cells need more energy provided by mitochondia to resist and repair UV damage. However, UV exposure increases ROS production leading to oxidative stress, that further damages mitochondrial function. Therefore, reducing oxidative stress and maintaining mitochondrial homeostasis is the key to preventing photoaging. FGRE can inhibit ROS production and enhance mitochondrial function, which can be considered as a photoprotection ingredient and used in skin care.

## 6. Reference

1. Gu, Y.; Han, J.; Jiang, C.; Zhang, Y. Biomarkers, oxidative stress and autophagy in skin aging. *Ageing Res Rev* **2020**, *59*, 101036, doi:10.1016/j.arr.2020.101036.
2. Rittié, L.; Fisher, G.J. Natural and sun-induced aging of human skin. *Cold Spring Harb Perspect Med* **2015**, *5*, a015370, doi:10.1101/cshperspect.a015370.

3. Naidoo, K.; Hanna, R.; Birch-Machin, M.A. What is the role of mitochondrial dysfunction in skin photoaging? *Experimental Dermatology* **2018**, *27*, 124-128, doi:https://doi.org/10.1111/exd.13476.
4. Sreedhar, A.; Aguilera-Aguirre, L.; Singh, K.K. Mitochondria in skin health, aging, and disease. *Cell Death & Disease* **2020**, *11*, 444, doi:10.1038/s41419-020-2649-z.
5. Djakpo, O.; Yao, W. Rhus chinensis and Galla Chinensis--folklore to modern evidence: review. *Phytother Res* **2010**, *24*, 1739-1747, doi:10.1002/ptr.3215.
6. Lee, J.J.; Cho, W.K.; Kwon, H.; Gu, M.; Ma, J.Y. *Galla rhois* exerts its antiplatelet effect by suppressing ERK1/2 and PLCβ phosphorylation. *Food Chem Toxicol* **2014**, *69*, 94-101, doi:10.1016/j.fct.2014.03.032.
7. Bao-ping, J. Study on Antioxidant Activities of Edible Plants and Medicinal Plants Common in China. *Food Science* **2006**.
8. Gorlach, S.; Fichna, J.; Lewandowska, U. Polyphenols as mitochondria-targeted anticancer drugs. *Cancer Letters* **2015**, *366*, 141-149, doi:https://doi.org/10.1016/j.canlet.2015.07.004.
9. Sharma, R.; Garg, P.; Kumar, P.; Bhatia, S.K.; Kulshrestha, S. Microbial Fermentation and Its Role in Quality Improvement of Fermented Foods. *Fermentation* **2020**, *6*, 106.
10. Xiang, H.; Sun-Waterhouse, D.; Waterhouse, G.I.N.; Cui, C.; Ruan, Z. Fermentation-enabled wellness foods: A fresh perspective. *Food Science and Human Wellness* **2019**, *8*, 203-243, doi:https://doi.org/10.1016/j.fshw.2019.08.003.
11. Lee, H.Y.; Ghimeray, A.K.; Yim, J.H.; Chang, M.S. Antioxidant, Collagen Synthesis Activity <i>in Vitro</i> and Clinical Test on Anti-Wrinkle Activity of Formulated Cream Containing <i>Veronica officinalis</i> Extract. *Journal of Cosmetics, Dermatological Sciences and Applications* **2015**, *05*, 45-51, doi:10.4236/jcdsa.2015.51006.
12. Shirzad, M.; Javad, H.; Elahe, M.; and Modarressi, M.H. Anti-elastase and anti-collagenase potential of Lactobacilli exopolysaccharides on human fibroblast. *Artificial Cells, Nanomedicine, and Biotechnology* **2018**, *46*, 1051-1061, doi:10.1080/21691401.2018.1443274.
13. Wu, Y.; Zhang, P.; Yang, H.; Ge, Y.; Xin, Y. Effects of demethoxycurcumin on the viability and apoptosis of skin cancer cells. *Molecular Medicine Reports* **2017**, *16*, 539-546, doi:10.3892/mmr.2017.6666.
14. Gu, X.; Ma, Y.; Liu, Y.; Wan, Q. Measurement of mitochondrial respiration in adherent cells by Seahorse XF96 Cell Mito Stress Test. *STAR Protocols* **2021**, *2*, 100245, doi:https://doi.org/10.1016/j.xpro.2020.100245.
15. Park, H.-H.; Park, N.-Y.; Kim, S.-G.; Jeong, K.-T.; Lee, E.-J.; Lee, E. Potential Wound Healing Activities of *Galla Rhois* in Human Fibroblasts and Keratinocytes. *The American Journal of Chinese Medicine* **2015**, *43*, 1625-1636, doi:10.1142/s0192415x15500925.
16. Leonard, W.; Zhang, P.; Ying, D.; Adhikari, B.; Fang, Z. Fermentation transforms the phenolic profiles and bioactivities of plant-based foods. *Biotechnology Advances* **2021**, *49*, 107763, doi:https://doi.org/10.1016/j.biotechadv.2021.107763.
17. Jeong, J.H.; Lee, C.Y.; Chung, D.K. Probiotic Lactic Acid Bacteria and Skin Health. *Critical Reviews in Food Science and Nutrition* **2016**, *56*, 2331-2337, doi:10.1080/10408398.2013.834874.

18. Hua, Z.; Wu, Q.; Yang, Y.; Liu, S.; Jennifer, T.G.; Zhao, D.; Fang, Y. Essential roles of ellagic acid-to-urolithin converting bacteria in human health and health food industry: An updated review. *Trends in Food Science & Technology* **2024**, *151*, 104622, doi:https://doi.org/10.1016/j.tifs.2024.104622.
19. Gu, Y.; Han, J.; Jiang, C.; Zhang, Y. Biomarkers, oxidative stress and autophagy in skin aging. *Ageing Research Reviews* **2020**, *59*, 101036, doi:https://doi.org/10.1016/j.arr.2020.101036.
20. Liu, H.-M.; Cheng, M.-Y.; Xun, M.-H.; Zhao, Z.-W.; Zhang, Y.; Tang, W.; Cheng, J.; Ni, J.; Wang, W. Possible Mechanisms of Oxidative Stress-Induced Skin Cellular Senescence, Inflammation, and Cancer and the Therapeutic Potential of Plant Polyphenols. *International Journal of Molecular Sciences* **2023**, *24*, 3755.
21. Lephart, E.D. Skin aging and oxidative stress: Equol's anti-aging effects via biochemical and molecular mechanisms. *Ageing Research Reviews* **2016**, *31*, 36-54, doi:https://doi.org/10.1016/j.arr.2016.08.001.
22. Papaccio, F.; D'Arino, A.; Caputo, S.; Bellei, B. Focus on the Contribution of Oxidative Stress in Skin Aging. *Antioxidants* **2022**, *11*, 1121.
23. Stout, R.; Birch-Machin, M. Mitochondria's Role in Skin Ageing. *Biology* **2019**, *8*, 29.
24. Kuffner, K.; Triebelhorn, J.; Meindl, K.; Benner, C.; Manook, A.; Sudria-Lopez, D.; Siebert, R.; Nothdurfter, C.; Baghai, T.C.; Drexler, K.; et al. Major Depressive Disorder is Associated with Impaired Mitochondrial Function in Skin Fibroblasts. *Cells* **2020**, *9*, 884.
25. Berger, F.; Ramírez-Hernández, M.a.H.; Ziegler, M. The new life of a centenarian: signalling functions of NAD(P). *Trends in Biochemical Sciences* **2004**, *29*, 111-118, doi:https://doi.org/10.1016/j.tibs.2004.01.007.
26. Wiley, Christopher D.; Velarde, Michael C.; Lecot, P.; Liu, S.; Sarnoski, Ethan A.; Freund, A.; Shirakawa, K.; Lim, Hyung W.; Davis, Sonnet S.; Ramanathan, A.; et al. Mitochondrial Dysfunction Induces Senescence with a Distinct Secretory Phenotype. *Cell Metabolism* **2016**, *23*, 303-314, doi:https://doi.org/10.1016/j.cmet.2015.11.011.
27. Chandhok, G.; Lazarou, M.; Neumann, B. Structure, function, and regulation of mitofusin-2 in health and disease. *Biological Reviews* **2018**, *93*, 933-949, doi:https://doi.org/10.1111/brv.12378.
28. Quintana-Cabrera, R.; Scorrano, L. Determinants and outcomes of mitochondrial dynamics. *Molecular Cell* **2023**, *83*, 857-876, doi:https://doi.org/10.1016/j.molcel.2023.02.012.
29. Gu, H.; Yang, K.; Wu, Q.; Shen, Z.; Li, X.; Sun, C. A link between protein acetylation and mitochondrial dynamics under energy metabolism: A comprehensive overview. *Journal of Cellular Physiology* **2021**, *236*, 7926-7937, doi:https://doi.org/10.1002/jcp.30461.
30. Quan, T.; Li, R.; Gao, T. Role of Mitochondrial Dynamics in Skin Homeostasis: An Update. *International Journal of Molecular Sciences* **2025**, *26*, 1803.
31. Ledrhem, M.; Nakamura, M.; Obitsu, M.; Hirae, K.; Kameyama, J.; Bouamama, H.; Gadhi, C.; Katakura, Y. Essential Oils Derived from Cistus Species Activate Mitochondria by Inducing SIRT1 Expression in Human Keratinocytes, Leading to Senescence Inhibition. *Molecules* **2022**, *27*, doi:10.3390/molecules27072053.