

# Protective Effects of Mogroside V on Oxidative Stress Induced by H<sub>2</sub>O<sub>2</sub> in Skin Fibroblasts

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**Purpose:** Damage caused by oxidative stress leads to the premature aging of cells. Mogrosides, the main active components of *Siraitia grosvenorii*, have strong antioxidant activity; however, it is unclear whether mogroside V (MV) exerts these effects in skin cells. This was investigated in the present study by evaluating the protective effects of MV against oxidative damage induced by hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) in skin fibroblasts.

**Methods:** Mouse skin fibroblasts (MSFs) were treated with H<sub>2</sub>O<sub>2</sub> and cell viability, total antioxidant capacity, reactive oxygen species (ROS) production, malondialdehyde (MDA) content, and antioxidant enzyme activity were assessed.

**Results:** Treatment with MV reduced the ROS level and MDA content in MSFs treated with H<sub>2</sub>O<sub>2</sub>. This was accompanied by increased superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) activities.

**Conclusion:** MV reduces H<sub>2</sub>O<sub>2</sub>-induced oxidative stress and enhances endogenous antioxidant activity in skin fibroblasts. Thus, MV can potentially be used as an ingredient in anti-aging cosmetic products.

**Keywords:** *Siraitia grosvenorii*, mogroside V, oxidative stress, antioxidant

## Introduction

Oxidative stress caused by reactive oxygen species (ROS) can have harmful effects when it exceeds the radical-scavenging capacity of cellular antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT).<sup>1-3</sup> Oxidative stress has been linked to the pathophysiology of various diseases and aging.<sup>4-6</sup> As the largest organ of the human body, skin is highly susceptible to the effects of environmental factors as it is in constant contact with the environment. Oxidative stress can accelerate aging and induce inflammation and melanin production in the skin. Fibroblasts maintain the structure and function of the dermis, ensuring proper skin functioning, including wound healing. Thus, fibroblasts play an important role in the process of skin aging, and they represent a potential therapeutic target to prevent this process.<sup>7,8</sup>

H<sub>2</sub>O<sub>2</sub> is a type of ROS that can easily cross the cell membrane to induce free radical production and lipid peroxidation, which inhibit cell proliferation and induce cell senescence and death. H<sub>2</sub>O<sub>2</sub> is widely used to induce oxidative stress in in vitro models because of its advantages of wide availability and stability.<sup>9,10</sup>

*Siraitia grosvenorii* is a type of gourd that is used in tea and soups in China. It is known as “fairy fruit” for its functions of clearing heat and reducing fire, relieving cough and phlegm, and dredging the intestines and stomach.<sup>11,12</sup> Mogrosides, which

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are the main active components of *S. grosvenorii*,<sup>13</sup> are nontoxic and have antioxidant, anti-inflammatory, antibacterial, and other biological properties.<sup>14,15</sup> Mogrosides were shown to inhibit hyperglycemia in a mouse model of diabetes induced by alloxan and showed strong oxygen free radical scavenging ability.<sup>16</sup> Pretreatment with mogroside extract increased SOD and GSH-Px activities and decreased malondialdehyde (MDA) content in ethanol-damaged L-02 liver cells, thereby reducing oxidative stress.<sup>17</sup>

Mogroside V (MV) is a tetracycline triterpenoid saponin with many hydroxyl groups that are responsible for its strong antioxidant activity.<sup>18</sup> The antioxidant capacity of MV against free radicals such as 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) along with its oxygen radical absorption capacity (ORAC), ferric reducing ability of plasma (FRAP), and capacity for inhibiting lipid oxidation have been demonstrated at the biochemical level in vitro.<sup>19</sup> MV increased the expression of antioxidant enzymes via nuclear factor-erythroid factor 2-related factor (Nrf2)-related antioxidant pathways to reduce ROS level and MDA content and alleviate ethanol-induced fatty liver injury in rats.<sup>20</sup> However, the antioxidant effects of MV on skin cells has not yet been reported. This was investigated in the present study using mouse skin fibroblasts (MSFs) treated with H<sub>2</sub>O<sub>2</sub> to induce oxidative stress in order to assess the therapeutic potential of MV for preventing skin aging.

## Methods

### Materials and Reagents

MSFs were obtained from the Chinese Academy of Sciences (Beijing, China); MV was purchased from Shanghai Yuanye Biotechnology Co. (Shanghai, China); Dulbecco's Modified Eagle's Medium (DMEM), fetal bovine serum (FBS), trypsin-ethylenediaminetetraacetic acid (EDTA), and penicillin/streptomycin were from Gibco (Grand Island, NY, USA). Cell lysis buffer; Cell Counting Kit-8 (CCK-8); ROS, MDA, SOD, GSH-Px, and CAT kits as well as the total antioxidant capacity assay kit with ABTS and FRAP were purchased from Beyotime Biotechnology Co. (Shanghai, China). A CO<sub>2</sub> constant temperature incubator was purchased from Shanghai Shengke Instrument and Equipment Co. (Shanghai, China; Model WJ-80A-II). The inverted fluorescence microscope was from Shanghai Tucsens Vision Technology Co. (Shanghai, China). The Infinite M200 PRO Fluorescent Plate Tester was from Tecan Trading Co.

(Shanghai, China). The TGL-16 refrigerated high-speed centrifuge was from Hunan Xiangyi Laboratory Instrument Development Co. (Hunan, China).

### Cell Culture

MSFs were cultured in DMEM containing 2% FBS, 1% fibroblast growth additive, and 1% penicillin/streptomycin in an incubator at 70–80% humidity, 37°C, and 5% CO<sub>2</sub>. The medium was changed every 2 days. When the cell confluence reached 80–90%, 0.05% trypsin-EDTA was used for digestion and cells were passaged at a volume ratio of 1:3.

### Cytotoxicity Analysis

The cytotoxicity of MV to MSFs was evaluated using CCK-8.<sup>21–23</sup> Cells were seeded in a 96-well plate at a density of 5×10<sup>3</sup> cells/well and cultured for 12 h. The original medium was discarded and different concentrations of MV or vitamin C (VC) were added. After 24 h of culture,<sup>24</sup> cells were lightly washed twice with phosphate-buffered saline (PBS) and 100 µL of serum-free DMEM was added to each well, followed by 10 µL of CCK-8 solution. The absorbance was measured at 450 nm after 2 h of culture.

### In vitro Model of H<sub>2</sub>O<sub>2</sub>-Induced Oxidative Stress

Cells were seeded in a 96-well plate at a density of 5×10<sup>3</sup> cells/well. After 12 h of culture, the original medium was discarded and H<sub>2</sub>O<sub>2</sub> diluted in serum-free medium to concentrations of 125, 250, 375, 500, 750, 1000, 1500, and 2000 µmol was added for 2 h. The CCK-8 assay was performed to determine the specific concentration of H<sub>2</sub>O<sub>2</sub> that induced cytotoxicity.

### Protective Effects of MV on H<sub>2</sub>O<sub>2</sub>-Induced Oxidative Stress in Cells

Cells were seeded in a 96-well plate at a density of 5×10<sup>3</sup> cells/well. After 12 h of culture, the cells were treated with 30, 60, and 90 µg/mL MV and 50 µg/mL VC for 24 h, then washed twice with PBS and treated with 1250 µmol H<sub>2</sub>O<sub>2</sub> solution for 2 h. Cell survival was evaluated with the CCK-8 assay.

### Measurement of ROS Content

Cells were seeded in a 6-well plate at a density of 1×10<sup>6</sup> cells/well and cultured in an incubator for 12 h until they

adhered to the wall of the plate. After adding MV for 24 h, H<sub>2</sub>O<sub>2</sub> was added for 2 h. After gentle washing with PBS, 2 mL of 10 µmol/L 2,7-dichlorodihydrofluorescein diacetate (DCFH-DA) diluted in serum-free medium was added, followed by incubation for 30 min; 12 h later, MV was added for 24 h. After light washing, the cells were stimulated with H<sub>2</sub>O<sub>2</sub> for 2 h and then incubated with 10 µmol/L DCFH-DA for 30 min. After washing 3 times with PBS, the optical density was measured with a microplate reader (488 nm excitation, 525 nm emission).

## Preparation of Cell Lysate

MSFs were seeded in a 6-well plate at a density of  $1 \times 10^6$  cells/well. After 12 h of culture, the cells were treated with MV and VC for 24 h, then stimulated with H<sub>2</sub>O<sub>2</sub> for 2 h. The cells were gently washed twice with PBS and placed on ice, and 100 µL of cell lysate was added. The lysed cells were centrifuged at 4°C for 10 min at 12,000 rpm. The supernatant was removed and stored at -80°C. As cell lysis buffer can contain peroxides with strong antioxidant capacity that could impact the measurement of total antioxidant capacity, the cell lysate used for this purpose was collected by adding cold PBS to the cells and freezing and thawing the suspension 3 times at temperatures ranging from -80°C to 37°C. Total antioxidant capacity, activity of antioxidant enzymes, and MDA content were measured according to the kit manufacturer's instructions.

## Statistical Analysis

At least 3 biological repetitions, each with 6 technical replicates, were performed for each experiment. All values are expressed as mean ± standard deviation. Data were processed using SPSS v22 software (IBM, Armonk, NY, USA). Differences between groups were analyzed by univariate analysis of variance and differences with  $P < 0.033$  were considered as statistically significant.

## Results

### Cell Viability Analysis

The cytotoxicity of MV and H<sub>2</sub>O<sub>2</sub> was evaluated with the CCK-8 assay. The effects of MV and VC on MSF cell viability are shown in Figure 1A and B. At MV concentrations between 7.8125 and 500 µg/mL, the survival rate of MSFs was >80%, indicating that it was nontoxic or only mildly toxic to the cells. At a concentration of 1000 µg/mL, the cell survival rate was 74.82%. Overall, there was a linear relationship between MV concentration and cell

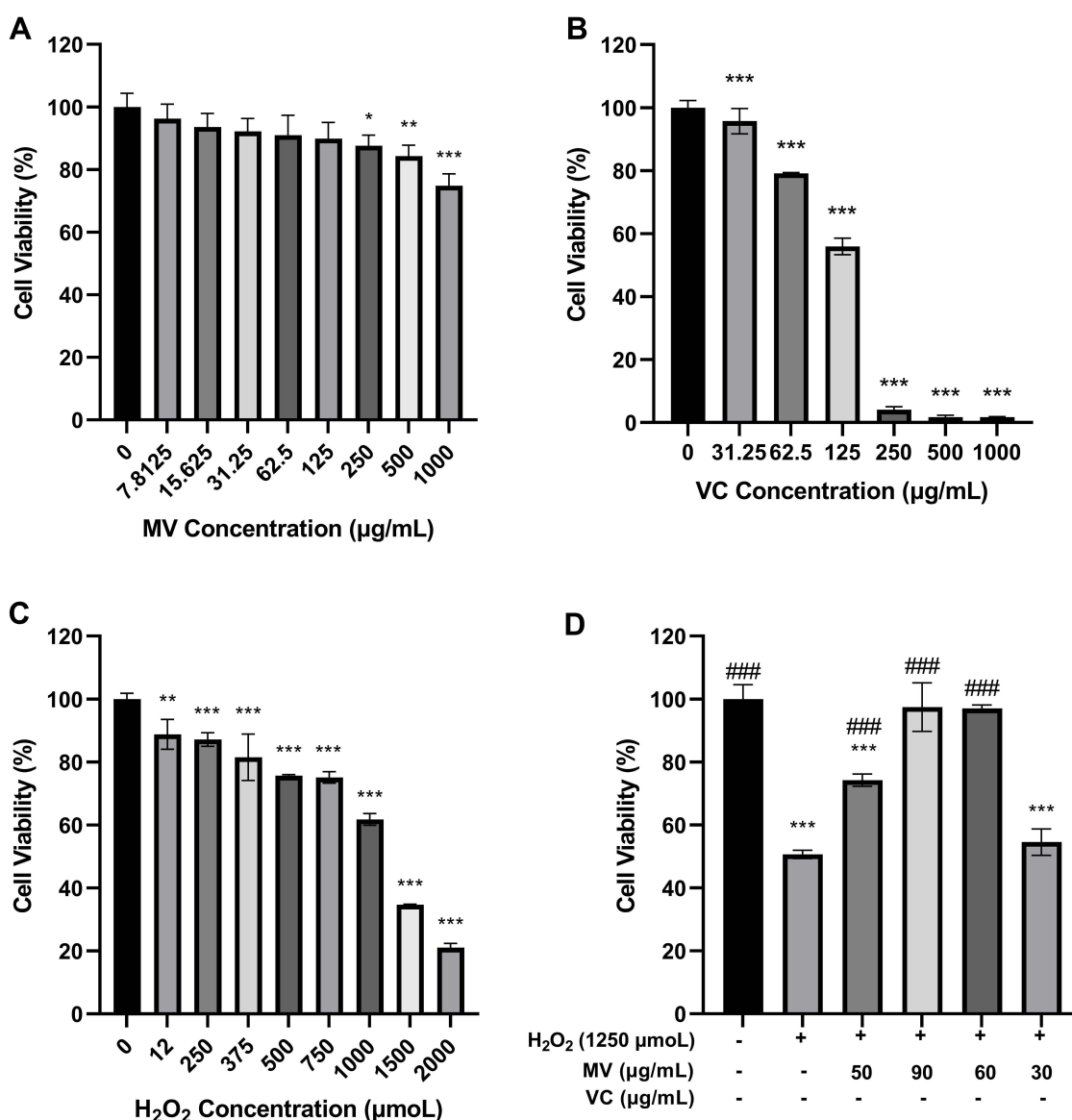
survival. Higher concentrations of VC were more toxic to the cells, which may have been attributable to its acidity. When the concentration of VC was <62.5 µg/mL, the cell survival rate was 80%; thus, the approximate concentrations of MV and VC that would yield a cell survival rate of 90% were calculated as 90 and 50 µg/mL, respectively. We therefore used 50 µg/mL VC and 30, 60, and 90 µg/mL MV for subsequent experiments comparing the effects of MV in cells treated with different concentrations of H<sub>2</sub>O<sub>2</sub> for 2 h.

The cell survival rates are shown in Figure 1C. There was an inverse relationship between H<sub>2</sub>O<sub>2</sub> concentration and cell survival. H<sub>2</sub>O<sub>2</sub> concentrations ≤375 µmol had little effect on the cell survival rate, which was >80%. A high cell survival rate suggests that there was no obvious oxidative damage while a low rate could indicate irreversible damage. Therefore, an H<sub>2</sub>O<sub>2</sub> concentration that would yield a cell survival rate of ~50% was selected to establish an H<sub>2</sub>O<sub>2</sub>-induced oxidative stress model: cells were treated with 1250 µmol H<sub>2</sub>O<sub>2</sub> for 2 h. The protective effects of MV on cells damaged by H<sub>2</sub>O<sub>2</sub> were examined (Figure 1D). Compared to the oxidative damage model group, cell viability was increased after 60 and 90 µg/mL MV treatment ( $P < 0.001$ ), and both concentrations of MV had more potent effects than VC. However, 30 µg/mL MV did not show significant protective effects.

Figure 2 shows the effects of MV on cells damaged by H<sub>2</sub>O<sub>2</sub> treatment. Before stimulation, the cells grew well, with a radiofibrous shape and tight arrangement. After stimulation, the cells were rounded, thick, damaged, and loosely arranged, and lacked a fibrous shape, and the number of cells was significantly reduced. However, cell morphology was significantly improved after MV and VC treatment. These results indicate that oxidative stress causes considerable damage to cell morphology that can be mitigated by MV.

### MV Suppresses H<sub>2</sub>O<sub>2</sub>-Induced ROS Production

DCFH-DA is a fluorescent probe for ROS detection that can permeate the cell membrane and is hydrolyzed into DCFH, which itself does not penetrate the cell membrane and is oxidized into fluorescent DCF by ROS. Thus, cellular ROS level can be determined by measuring DCF fluorescence. MSFs were stained with DCFH-DA (Figure 3). Compared to the blank control group, intracellular ROS level was increased in the H<sub>2</sub>O<sub>2</sub>-treated group. Application of 60 and



**Figure 1** (A) Effects of different concentrations of MV on cell viability (n=6); (B) Effects of different concentrations of VC on cell viability (n=6); (C) Effects of different concentrations of H<sub>2</sub>O<sub>2</sub> on cell viability (n=6); (D) Cell viability was measured by CCK8 after 24 h of MV or VC pretreatment and 2 h of H<sub>2</sub>O<sub>2</sub> stimulation.

**Notes:** ANOVA test was performed to determine statistical significance. Compared with the blank group, \**P* < 0.033, \*\**P* < 0.002, \*\*\**P* < 0.001. Compared with the damage model group, ###*P* < 0.001. When *P* > 0.033, values do not have a common mark (\*, #).

**Abbreviations:** MV, mogroside V; VC, vitamin C; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide.

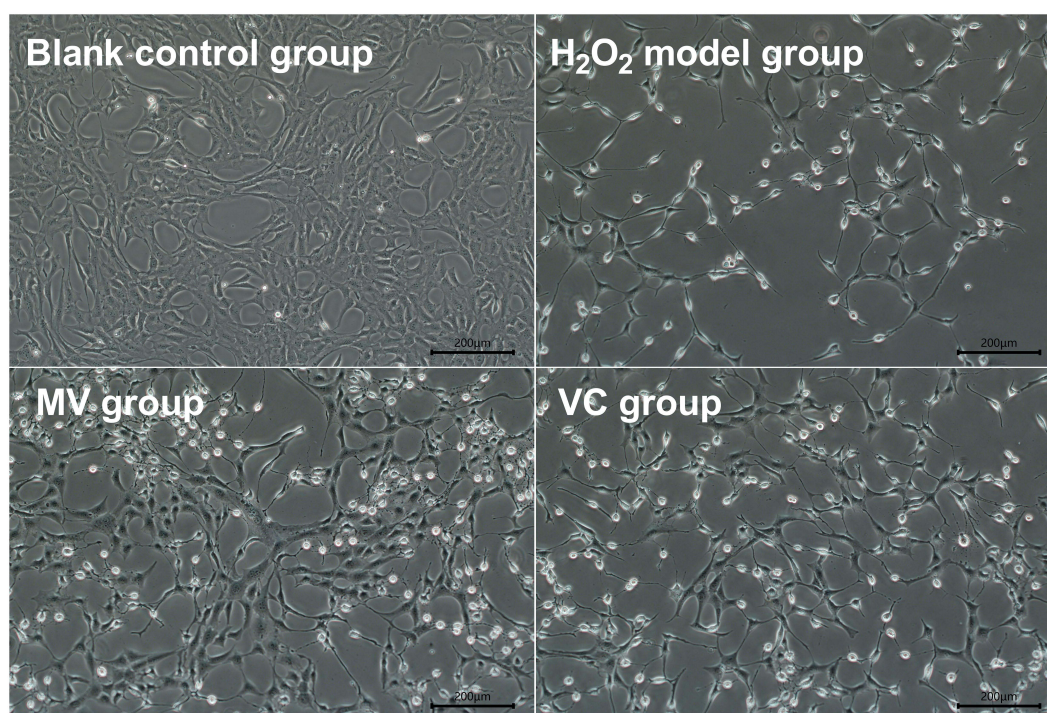
90 µg/mL MV and 50 µg/mL VC reduced intracellular ROS level (*P* < 0.001; Figure 3B), indicating that MV can suppress ROS induced by exposure to H<sub>2</sub>O<sub>2</sub>.

## Effects of MV on MDA Content and Total Antioxidant Capacity in H<sub>2</sub>O<sub>2</sub>-Treated Cells

Oxidative stress in cells leads to lipid peroxidation. Oxidized fatty acids are gradually broken down into various

compounds including MDA. Therefore, MDA content reflects the degree of lipid oxidation and a lower MDA content indicates a higher antioxidant capacity. We found that MV reduced MDA content in cells damaged by H<sub>2</sub>O<sub>2</sub> (*P* < 0.033; Figure 4A), suggesting that it enhanced cellular antioxidant capacity. ABTS is an artificial free radical that is used for direct assessment of free radical scavenging activity whereas FRAP is a measure of the Fe<sup>3+</sup>-reducing ability of a sample.<sup>25,26</sup> We next examined the effects of MV on the





**Figure 2** Effects of MV on state of  $H_2O_2$ -induced oxidative damage cells (40X).  
**Abbreviations:** MV, mogroside V; VC, vitamin C;  $H_2O_2$ , hydrogen peroxide.

total antioxidant capacity of  $H_2O_2$ -treated cells and found that treatment with 90 and 60  $\mu\text{g/mL}$  MV significantly increased total antioxidant capacity ( $P < 0.001$ ; Figure 4B and C); moreover, the effects were superior to those of VC although they were not observed at a low MV concentration.

## SOD, CAT, and GSH-Px Activities

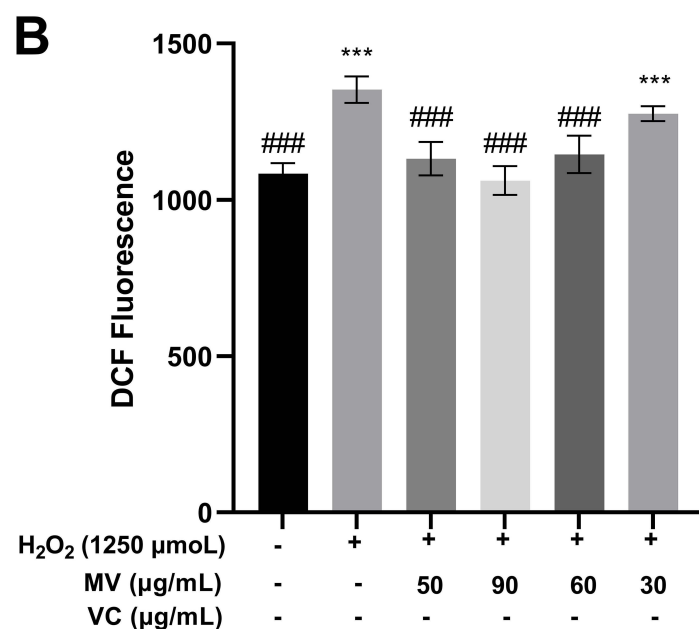
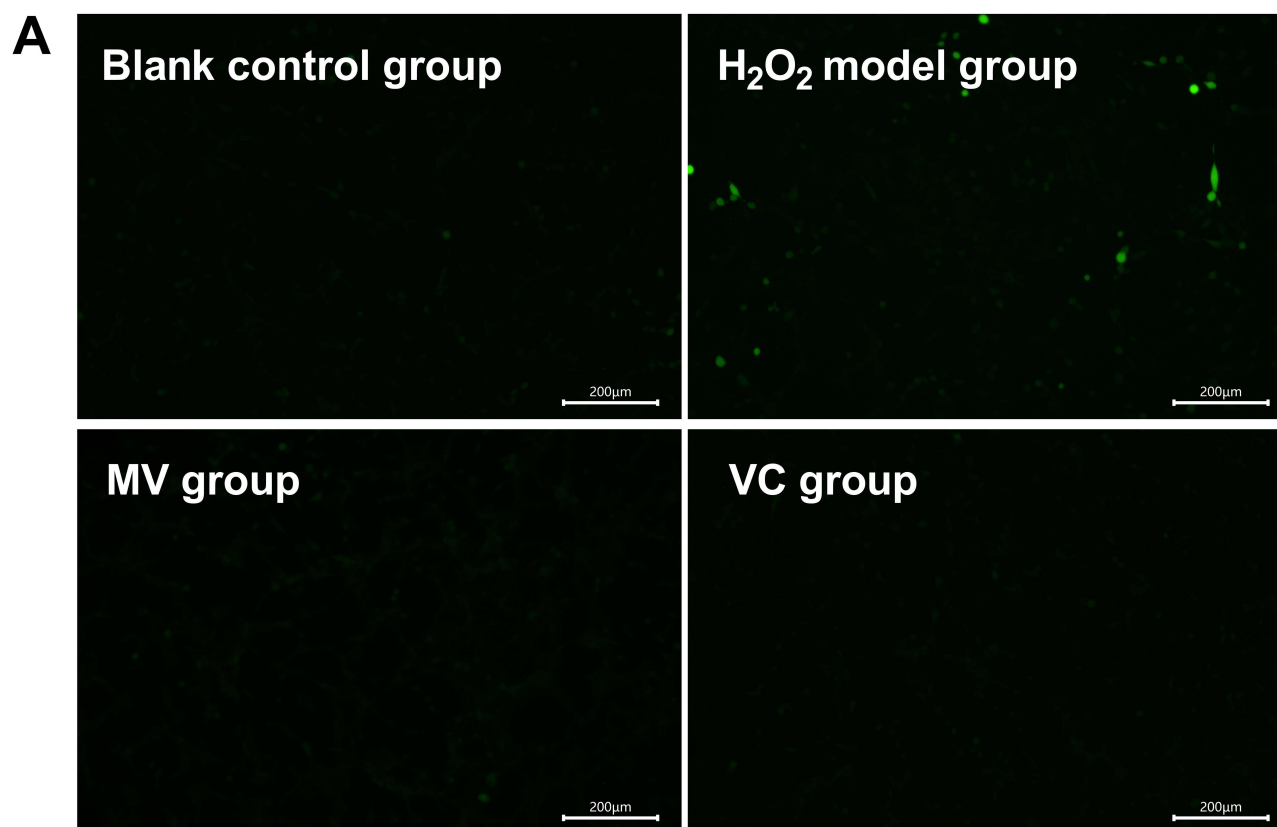
We evaluated the effects of MV on the activity of antioxidant enzymes in cells exposed to  $H_2O_2$ . Compared to the oxidative stress model group, MV at 3 different concentrations significantly increased CAT activity ( $P < 0.001$ ); 60 and 90  $\mu\text{g/mL}$  MV increased SOD activity ( $P < 0.001$ ); and 90  $\mu\text{g/mL}$  MV increased GSH-Px activity ( $P < 0.001$ ) in a concentration-dependent manner (Figure 5).

## Discussion

Oxidative stress leads to the production of excessive ROS that directly or indirectly damage DNA and proteins, causing cell death. Skin aging, dryness, and pigmentation are closely related to an imbalance between skin oxidation and antioxidant homeostasis; some skin disorders such as atopic dermatitis and freckling have also been linked to oxidative damage.<sup>27</sup>

Natural antioxidants such as polyphenols, flavonoids, polysaccharides, and amino acids are accessible and have high activity, biocompatibility, and safety. *S. grosvenorii* is a plant native to Guangxi, China, that has been used for medicinal purposes for >300 years.<sup>28</sup> Mogrosides are the main bioactive components of *S. grosvenorii* and their antioxidant capacity has been the focus of many studies. The inhibitory effect of MV on free radicals—mainly  $O_2^-$ , OH, and  $H_2O_2$ —has been demonstrated in vitro.<sup>29</sup> Mogrosides were shown to exert an antioxidant effect in insulinoma cells by reducing the intracellular ROS level and regulating the expression of genes related to glucose metabolism under palmitic acid-induced oxidative stress.<sup>30</sup> A study on the antioxidant and anti-glycosylation activity of *S. grosvenorii* extracts showed that mogrosides are  $H_2O_2$  free radical scavengers that also exert strong effects on DPPH and ABTS.<sup>31</sup>

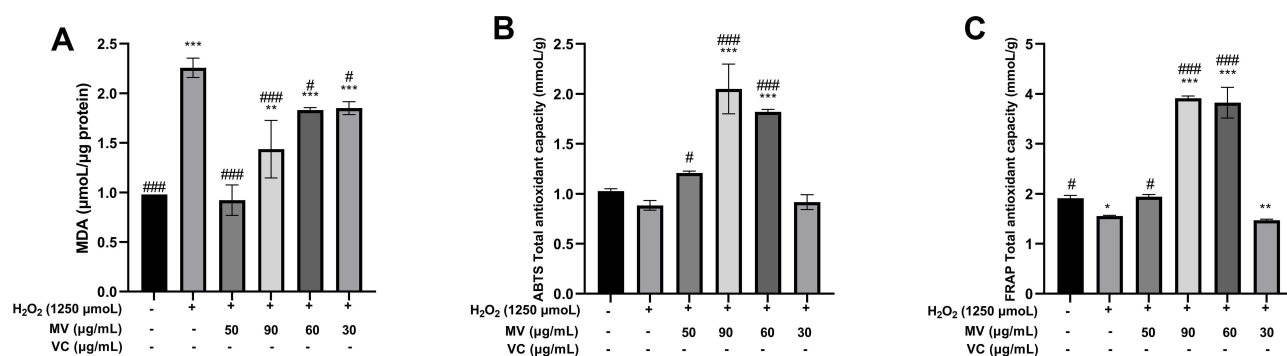
In this study, we evaluated the antioxidant effect of MV in a cell-based model of  $H_2O_2$ -induced oxidative stress. MSFs were treated with 1250  $\mu\text{mol}$   $H_2O_2$  for 2 h to establish the model. The results showed that MV concentration  $\leq 500$   $\mu\text{g/mL}$  was not cytotoxic. Similar to the results of previous studies, treatment with MV enhanced the antioxidant capacity of MSFs exposed to  $H_2O_2$ , and ROS were eliminated.



**Figure 3 (A)** Effects of MV on ROS production induced by H<sub>2</sub>O<sub>2</sub> stimulation (40X); **(B)** Effects of MV on ROS content in MSF cells stimulated by H<sub>2</sub>O<sub>2</sub> (n=6).

**Notes:** ANOVA test was performed to determine statistical significance. Compared with the blank group, \*\*\**P* < 0.001. Compared with the damage model group, ####*P* < 0.001. When *P* > 0.033, values do not have a common mark (\*, #).

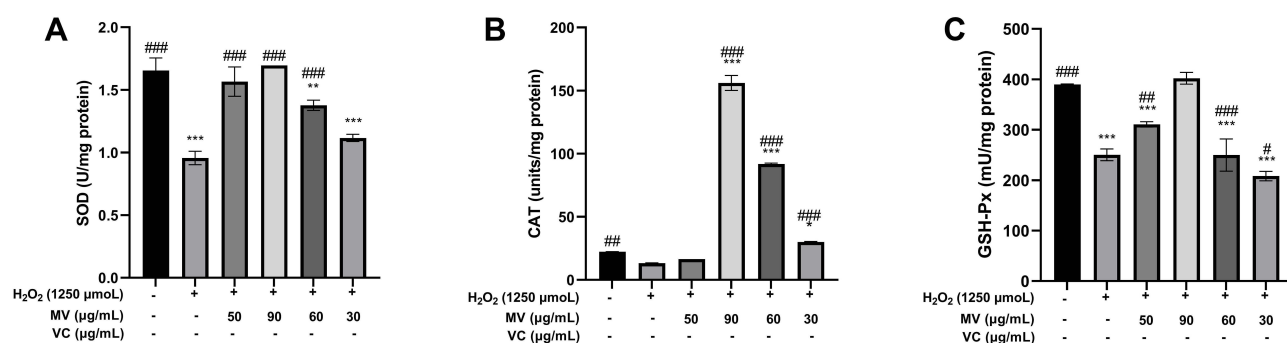
**Abbreviations:** MV, mogroside V; VC, vitamin C; ROS, reactive oxygen species; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide.



**Figure 4 (A)** Effects of MV on MDA content in H<sub>2</sub>O<sub>2</sub>-induced oxidative damage MSF cells (n=6); **(B)** Effects of MV on total antioxidant capacity (ABTS) of H<sub>2</sub>O<sub>2</sub>-induced oxidative damage MSF cells (n=6); **(C)** Effects of MV on total antioxidant capacity (FRAP) of H<sub>2</sub>O<sub>2</sub>-induced oxidative damage MSF cells (n=6).

**Notes:** ANOVA test was performed to determine statistical significance. Compared with the blank group, \**P* < 0.033, \*\**P* < 0.002, \*\*\**P* < 0.001. Compared with the damage model group, #*P* < 0.033, ###*P* < 0.001. When *P* > 0.033, values do not have a common mark (\*, #).

**Abbreviations:** MV, mogroside V; VC, vitamin C; MDA, malondialdehyde; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide.



**Figure 5 (A)** Effects of MV on SOD activity of H<sub>2</sub>O<sub>2</sub>-induced oxidative damage cells (n=6); **(B)** Effects of MV on CAT activity of H<sub>2</sub>O<sub>2</sub>-induced oxidative damage cells (n=6); **(C)** Effects of MV on GSH-Px activity of H<sub>2</sub>O<sub>2</sub>-induced oxidative damage cells (n=6).

**Notes:** ANOVA test was performed to determine statistical significance. Compared with the blank group, \**P* < 0.033, \*\**P* < 0.002, \*\*\**P* < 0.001. Compared with the damage model group, #*P* < 0.033, ##*P* < 0.002, ###*P* < 0.001. When *P* > 0.033, values do not have a common mark (\*, #).

**Abbreviations:** MV, mogroside V; VC, vitamin C; SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide.

MV has been shown to reduce oxidative stress by suppressing ROS production and increasing the expression of SOD, CAT, sirtuin 1, and oxidative stress- and mitochondria-related genes, thereby inhibiting oocyte aging in vitro.<sup>32,33</sup> SOD, CAT, and GSH-Px are the 3 main enzymes in the cellular enzymatic antioxidant system. SOD reacts with  $\cdot\text{O}_2^-$  to produce H<sub>2</sub>O<sub>2</sub>, which is broken down into water and oxygen by CAT and peroxidase, preventing the formation of the damaging  $\cdot\text{OH}$  radical. GSH-Px converts lipid peroxides into nontoxic products and uses GSH to convert H<sub>2</sub>O<sub>2</sub> into water or organic alcohol.<sup>34</sup> Thus, the activities of SOD, CAT, and GSH-Px can serve as indicators of the antioxidant capacity of MV. After MV treatment, the activities of the 3 enzymes in MSFs was significantly increased, with a concomitant decrease in MDA content compared to the oxidative stress model group, indicating that MV has antioxidant capacity. The cellular antioxidant defense system also includes non-enzymatic mechanisms<sup>35</sup> involving lipid

(carotenoids, vitamin E, etc.) and water-soluble (glutathione S-transferase, VC, proteins, and trace elements such as selenium and zinc) antioxidants.<sup>36,37</sup> As the 2 systems interact, the effects of MV at the same or different concentrations have different effects on SOD, CAT, and GSH-Px.

Other studies on the antioxidant effects of plant extracts on skin cells (such as fibroblasts and keratinocytes) have shown that they promote resistance to oxidative stress damage caused by radiation and other factors, and have revealed the molecular mechanism of resistance to oxidative stress and skin aging. Both water and alcohol extracts of *Spatholobus suberectus* stems inhibited ultraviolet B (UVB)-induced ROS production and cellular damage in HaCaT cells, and blocked UVB-induced phosphorylation of mitogen-activated protein kinase, nuclear factor (NF)- $\kappa\text{B}$ , and c-Jun, suggesting a strong anti-aging potential.<sup>38</sup> By reducing ROS production, *Melissa officinalis* extract reduced oxidative

damage to the skin caused by ultraviolet radiation and blue light.<sup>39</sup> Atractyligenin, a terpenoid isolated from coffee silverskin, reduced UVA-induced oxidative damage by inhibiting intracellular ROS production.<sup>40</sup> Red and white wine extracts were shown to have significant antioxidant and anti-aging activity in H<sub>2</sub>O<sub>2</sub>-treated fibroblasts exposed to stressors, as reflected by CAT and  $\beta$ -galactosidase activities.<sup>24</sup> The results of our study demonstrate that MV helps skin fibroblasts resist oxidative stress by promoting the elimination of ROS and MDA by antioxidant enzymes, although this remains to be confirmed in vivo.

## Conclusion

The results of this study demonstrate that MV scavenges free radicals to promote oxidative stress resistance in skin fibroblasts through regulation of antioxidant enzymes. This provides an empirical basis for the application of MV and *S. grosvenorii* as an anti-aging ingredient in cosmetic products. Specifically, it can be used to prevent skin aging or lesions caused by oxidative stress. However, additional studies are required to clarify the underlying molecular mechanism using omics and other technologies.

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## Disclosure

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