Submitted: 04 December, 2024 Accepted: 06 March, 2025 Published: 08 May, 2025 DOI:10.22514/sv.2025.069

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Signa Vitae

ORIGINAL RESEARCH

Dendrobine promotes cardiomyocyte proliferation and inhibits apoptosis and inflammation in an *in vitro* acute myocardial infarction model

Qian Liu[1], Li Lin[1,*], Shudan Cao[2], Peilun Jin[1]

[1]Department of Emergency Medicine, Lishui Hospital of TCM, 323000 Lishui, Zhejiang, China
[2]Department of Endocrine, Shanghai Songjiang District Si Jing Hospital, 201601 Shanghai, China

***Correspondence**
li_lin0829@163.com
(Li Lin)

Abstract

Background: Acute myocardial infarction (AMI) is a serious condition caused by the sudden blockage of a coronary artery, leading to heart tissue damage. The increasing number of AMI cases, particularly in younger individuals as a result of unhealthy lifestyles, highlights the demand for innovative treatments. Dendrobine, a compound from Dendrobium, has multiple biological activities, such as suppressing oxidative stress, inflammation and cell death. **Methods**: An *in vitro* AMI model was established using H9C2 rat cardiomyocytes subjected to hypoxia/reoxygenation (H/R) conditions. The effects of dendrobine on cardiomyocyte proliferation were assessed using Cell Counting Kit (CCK)8 assays and EdU staining. Apoptosis was evaluated by flow cytometry and Western blot. Inflammatory responses were measured through Enzyme-Linked Immunosorbent Assay (ELISA) and Immunoblot, and the involvement of the Nuclear factor erythroid 2-related factor 2 (Nrf2)/Kelch-like ECH-associated protein 1 (Keap1) signaling pathway was examined using Western blot. **Results**: Dendrobine significantly promoted cardiomyocyte proliferation under H/R conditions, inhibited apoptosis in H9C2 cells, and effectively suppressed the inflammatory response. Additionally, dendrobine enhanced the activation of the Nrf2/Keap1 signaling pathway. **Conclusions**: Dendrobine exerts significant cardioprotective effects in an *in vitro* AMI model by promoting cell proliferation, suppressing programmed cell death and inflammation and regulating the Nrf2/Keap1 pathway. Therefore, dendrobine holds potential as a therapeutic agent for AMI intervention.

Keywords

Dendrobine; Acute myocardial infarction; Hypoxia/reoxygenation; Cardioprotection; Nrf2/Keap1 signaling

1. Introduction

Acute myocardial infarction (AMI) is a severe cardiovascular condition caused by the sudden occlusion of a coronary artery, leading to a rapid reduction in blood flow to the myocardium [1]. The occurrence of ischemia leads to a lack of oxygen supply, which can ultimately result in tissue necrosis if the condition persists. AMI can trigger life-threatening complications such as cardiogenic shock, arrhythmias, cardiac rupture and heart failure, which significantly impair cardiac function [2]. Research on the prevalence of AMI reveals a significant rise in cases as individuals age, alongside a concerning pattern of AMI occurrences in younger age groups [3]. This shift is largely attributed to the prevalence of modern lifestyle factors such as poor dietary habits, physical inactivity, smoking and stress. Despite the progress made in therapies such as percutaneous coronary intervention, AMI continues to be a prominent factor contributing to death on a worldwide scale. The enduring complications following AMI, such as heart failure, present considerable obstacles and difficulties [4]. There is an urgent need to explore new therapeutic strategies that can mitigate myocardial damage and improve patient outcomes. Natural compounds derived from medicinal plants have gained attention for their potential benefits in cardiovascular diseases. Out of these, dendrobine, a sesquiterpene alkaloid derived from Dendrobium, a genus of orchids commonly employed in traditional medicine, has exhibited potential.

Dendrobine has been documented to have various biological activities, including neuroprotective effects by rescuing cognitive dysfunction in diabetic encephalopathy, anti-inflammatory and anti-apoptotic effects in osteoclast differentiation and neuroprotection in Parkinson's disease models [5]. It demonstrates anti-cancer characteristics by preventing the migration and spread of cancer cells [6, 7]. These diverse effects suggest that dendrobine could offer therapeutic potential in AMI, where oxidative

stress, inflammation and apoptosis are key factors. Its potential cardioprotective effects, particularly in hypoxia/reoxygenation (H/R)-induced injury, which simulates the ischemia/reperfusion injury seen in AMI, warrant further investigation. Oxidative damage, inflammation, and apoptosis in cardiomyocytes are consequences of H/R injury, which renders it a pertinent model for investigating AMI. Despite these promising findings, the role of dendrobine in AMI is not fully understood.

This study aims to elucidate the cardioprotective effects of dendrobine in an *in vitro* model of AMI. More specifically, it will investigate how dendrobine affects the proliferation, apoptosis, and inflammation of cardiomyocytes in the setting of H/R. The findings could potentially lead to the creation of innovative treatment approaches for AMI and provide insights into the potential of dendrobine as a cardioprotective agent.

2. Materials and methods

2.1 Cell Culture and hypoxia/reoxygenation (H/R) treatment

H9C2 rat cardiomyocytes were purchased from American Type Culture Collection (ATCC) and cultured in Dulbecco's Modified Eagle's Medium (DMEM) (Beyotime, ST144, Beijing, China) supplemented with 10% Fetal Bovine Serum (FBS) (Beyotime, C0221, Beijing, China) at 37 °C in a 5% CO_2 incubator. For H/R experiments, cells were subjected to hypoxia (1% O_2, 94% N_2, 5% CO_2) for 16 h followed by reoxygenation under normoxic conditions (21% O_2, 5% CO_2) for 2 h.

2.2 Dendrobine treatment

Dendrobine was obtained from Beyotime (S6001, Beijing, China) and dissolved in Dimethyl Sulfoxide (DMSO) (Beyotime, S0001, Beijing, China) to prepare stock solutions. During the reoxygenation phase, the cells were exposed to dendrobine at concentrations of 5, 10 and 20 μmol/L.

2.3 Cell viability assay

Cell viability was assessed using the CCK-8 assay (Beyotime, C0040, Beijing, China). H9C2 cells were plated onto 96-well plates and subjected to the specified treatment. CCK-8 reagent was added to each well, and absorbance was measured at 450 nm using a microplate reader (Thermo Fisher, Multiskan FC, Vantaa, Finland).

2.4 EdU proliferation assay

Following the treatment, the cells were exposed to 5-Ethynyl-2′-deoxyuridine (EdU) (Beyotime, C0071S, Beijing, China) for a period of 2 h, then treated with 4% paraformaldehyde (Beyotime, P0099, Beijing, China) and subsequently stained. The nuclei were counterstained with 4′,6-Diamidino-2-phenylindole (DAPI) (Beyotime, C1005, Beijing, China). Images were captured using a fluorescence microscope (Zeiss, Axio A1, Oberkochen, BRW, Germany) and EdU-positive cells were quantified.

2.5 Flow cytometry

Apoptosis was analyzed by Flow Cytometry (FCM) using the Annexin Fluorescein Isothiocyanate-V (V-FITC, where "V" depends on context, *e.g.*, Annexin V-FITC) kit (Beyotime, C1062, Beijing, China). After treatment, cells were harvested, stained with Annexin V-FITC and Propidium Iodide (PI), and analyzed on a flow cytometer (BD, FACSCanto II, San Jose, CA, USA). Data were processed using FlowJo software (BD, 10.6.2, Ashland, OR, USA).

2.6 Immunoblot

Proteins were separated by Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) and transferred onto Polyvinylidene Difluoride (PVDF) membrane (Millipore, IPVH00010). Membranes were blocked with 5% non-fat milk and incubated overnight at 4 °C with the following primary antibodies: Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH) (Abcam, ab9485, 1:5000, Cambridge, UK), anti-BCL2-Associated X protein (Bax) (Abcam, ab182733, 1:1000, Cambridge, UK), anti-B-cell lymphoma 2 (BCL-2) (Abcam, ab196495, 1:1000, Cambridge, UK), anti-cleaved caspase-3 (Abcam, ab32042, 1:1000, Cambridge, UK), anti-Nrf2 (Abcam, ab62352, 1:1000, Cambridge, UK), and anti-Keap1 (Abcam, ab139729, 1:1000, Cambridge, UK), anti-p65 (Abcam, ab32536, 1:1000, Cambridge, UK), anti-p-p65 (Abcam, ab76302, 1:500, Cambridge, UK), anti-caspase-1 (Abcam, ab207802, 1:1000, Cambridge, UK), anti-Apoptosis-Associated Speck-like Protein Containing a CARD (ASC) (Abcam, ab283684, 1:1000, Cambridge, UK), and anti-NLR Family Pyrin Domain Containing 3 (NLRP3) (Abcam, Cambridge, UK, ab263899, 1:1000). After washing, membranes were incubated with Horseradish Peroxidase (HRP)-conjugated secondary antibodies (Beyotime, A0208, 1:2000, Beijing, China) for 1 h. Bands were visualized using an Enhanced Chemiluminescence (ECL) detection kit (Beyotime, P0018, Beijing, China).

2.7 ELISA

The levels of Tumor Necrosis Factor (TNF)-α, Interleukin (IL)-6 and IL-1β in cell culture supernatants were quantified using ELISA kits (Beyotime, PI330, PI326, PI303, Beijing, China). The absorbance at 450 nm was determined by utilizing a microplate reader from Thermo Fisher, and the levels of cytokines were then determined by extrapolating from standard curves.

2.8 Statistical analysis

All data are presented as mean $\pm$ Standard Deviation (SD). Statistical analyses were performed using GraphPad 8.0 (GraphPad Software, San Diego, CA, USA). Differences between groups were assessed using one-way Analysis of Variance (ANOVA) followed by Tukey's *post-hoc* test. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1 Dendrobine promotes proliferation in H9C2 cells under hypoxia/reoxygenation (H/R) conditions

To assess whether dendrobine could enhance cell proliferation under H/R conditions, H9C2 cells were used. The molecular structure of dendrobine was shown in Fig. 1A. Exposure of H9C2 cells to H/R conditions resulted in a notable decrease in both cell viability and growth, as indicated by a decrease in proliferation ability in the CCK-8 assay (Fig. 1B) and fewer EdU-positive cells (Fig. 1C,D). However, when treated with dendrobine, cell proliferation improved, and there was a noticeable increase in the number of proliferating cells (Fig. 1B–D). Therefore, Den effectively counteracts the inhibitory effects of H/R on cardiomyocyte proliferation.

3.2 Dendrobine inhibits apoptosis in H9C2 cells under hypoxia/reoxygenation (H/R) conditions

To further determine if dendrobine could reduce apoptosis in H9C2 cells under H/R conditions, FCM assays were conducted. H/R conditions led to a marked increase in apoptosis in H9C2 cells, with more cells undergoing programmed cell death (Fig. 2A). This was followed by increased expression of pro-apoptotic proteins such as Bax and cleaved caspase-3, along with a reduction in the levels of the anti-apoptotic protein BCL-2 (Fig. 2B). In contrast, dendrobine treatment significantly reduced the number of apoptotic cells and altered the expression of these proteins, decreasing Bax and cleaved caspase-3 while increasing BCL-2 (Fig. 2A,B). These results indicate that dendrobine plays a role in safeguarding cardiomyocytes against apoptosis induced by hypoxia/reoxygenation.

3.3 Dendrobine suppresses inflammation in H9C2 cells under hypoxia/reoxygenation (H/R) conditions

We then investigate whether dendrobine is able to alleviate the inflammatory reaction triggered H/R. H9C2 cells subjected to H/R exhibited a significant increase in pro-inflammatory cytokines TNF-α, IL-6 and IL-1β, indicating an elevated inflammatory response (Fig. 3). However, treatment with dendrobine significantly reduced the levels of these cytokines, showing its strong anti-inflammatory properties (Fig. 3A). Immunoblot also indicated that the phosphorylation levels of p65 and expression of NLRP3, ASC, and caspase-1 were increased by H/R treatment but further decreased after dendrobine treatment

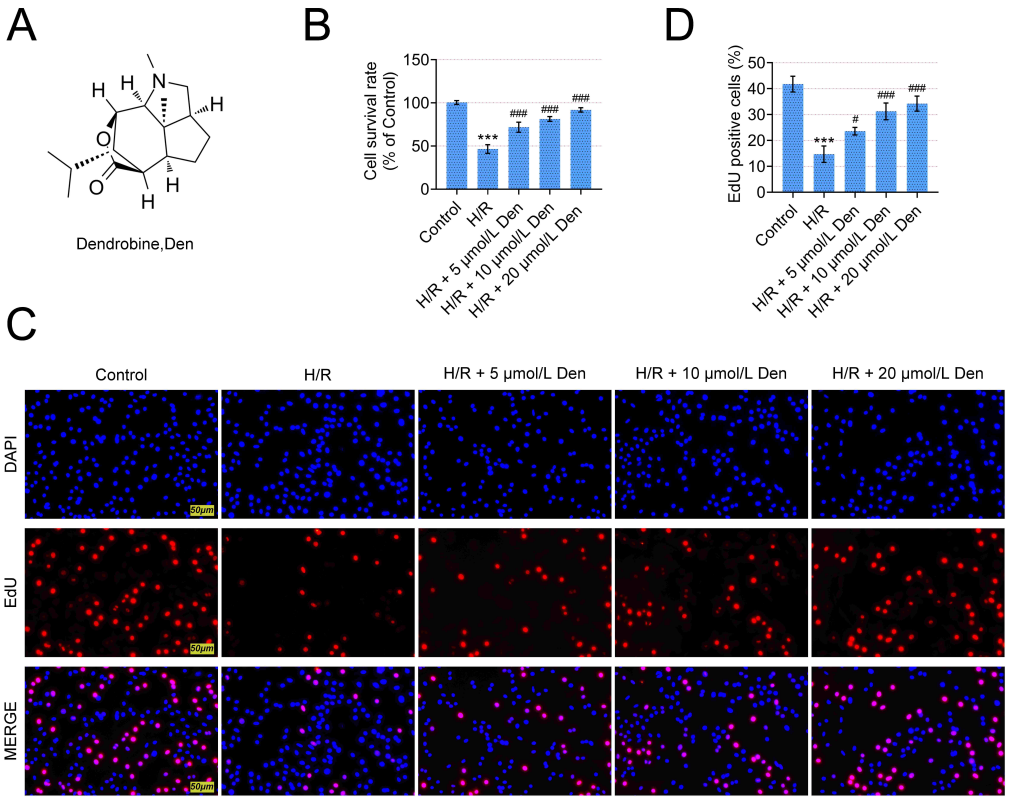

FIGURE 1. Dendrobine (Den) promotes proliferation in H9C2 cells under hypoxia/reoxygenation (H/R) conditions. (A) The chemical structure of dendrobine (Den). (B) Cell survival rate was measured by the CCK8 assay. H9C2 cells were treated with H/R alone or in combination with various concentrations of Den (5, 10, 20 μmol/L). The results are presented as a percentage of control cells. (C) Representative images of EdU staining in H9C2 cells treated under the same conditions for 24 h. DAPI was used to stain the nuclei, and EdU incorporation was used as an indicator of cell proliferation. Images show DAPI (blue), EdU (red) and the merged images. Scale bar = 50 μm. (D) Quantification of EdU-positive cells expressed as a percentage of the total cell population. Data are presented as mean ± SD. ***$p < 0.001$ *vs.* control group; #$p < 0.05$, and ###$p < 0.001$ *vs.* H/R group. EdU: 5-Ethynyl-2′-deoxyuridine; DAPI: 4′,6-Diamidino-2-phenylindole.

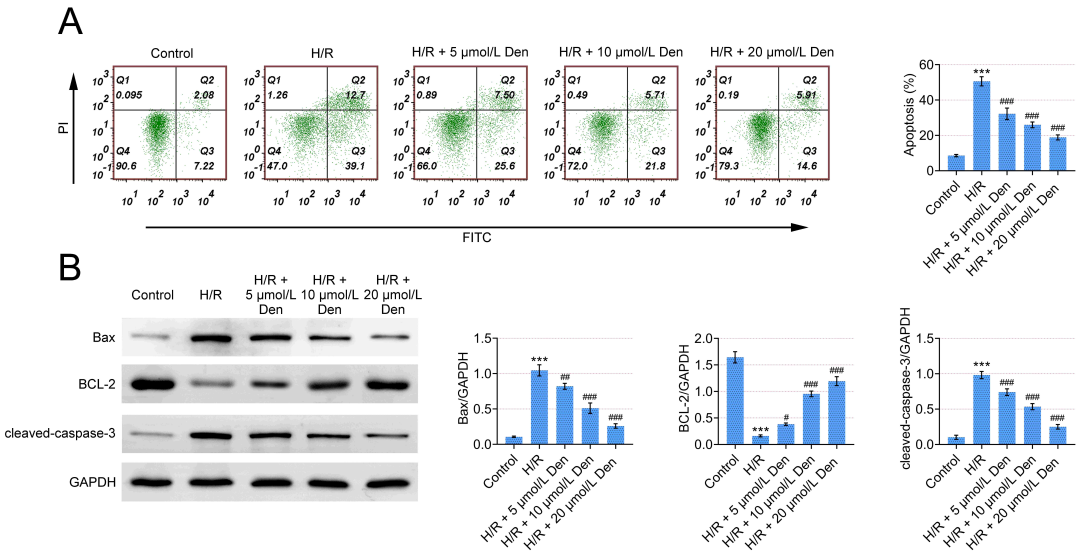

FIGURE 2. Dendrobine (Den) inhibits apoptosis in H9C2 cells under hypoxia/reoxygenation (H/R) conditions. (A) Flow cytometry analysis of apoptosis in H9C2 cells treated with H/R alone or in combination with various concentrations of Den (5, 10, 20 μmol/L) for 24 h. The percentage of apoptotic cells was quantified. (B) Immunoblot analysis of apoptosis-related proteins, including Bax, BCL-2 and cleaved caspase-3, in H9C2 cells under the same treatment conditions for 24 h. The expression levels of these proteins were normalized to GAPDH and quantified. Data are presented as mean ± SD. ***$p < 0.001$ *vs.* control group; #$p < 0.05$, ##$p < 0.01$ and ###$p < 0.001$ *vs.* H/R group. PI: Propidium Iodide; FITC: Fluorescein Isothiocyanate; Bax: BCL2-Associated X protein; BCL-2: B-cell lymphoma 2; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase.

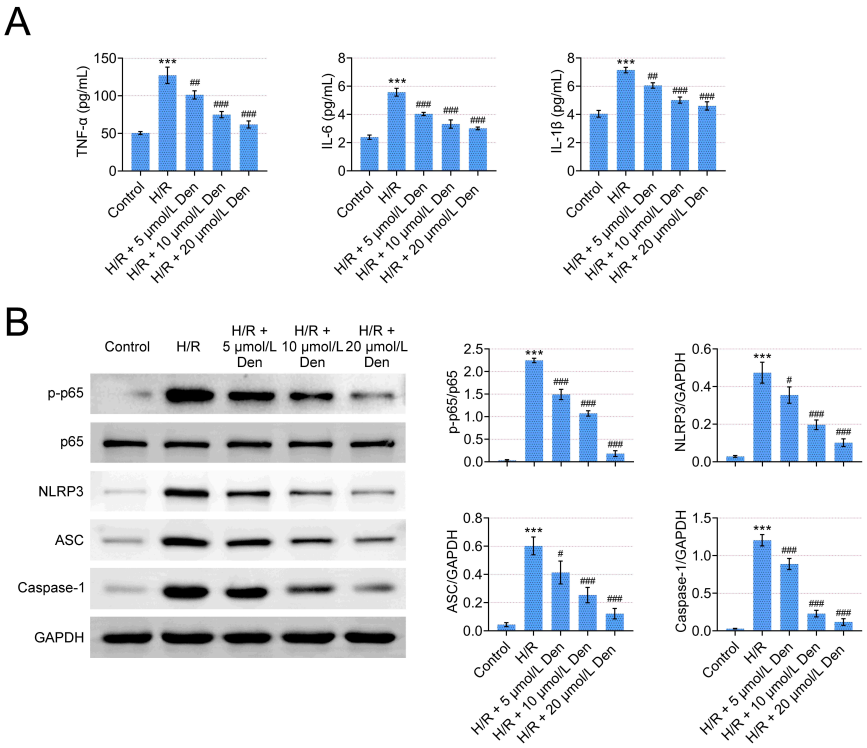

FIGURE 3. Dendrobine (Den) suppresses inflammation in H9C2 cells under hypoxia/reoxygenation (H/R) conditions. (A) The levels of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β in H9C2 cells were measured using ELISA after treatment with H/R alone or in combination with various concentrations of Den (5, 10, 20 μmol/L) for 24 h. (B) The expression of p-p65, p65, NLRP3, ASC, and caspase-1 in H9C2 cells were measured using Immunoblot after treatment with H/R alone or in combination with various concentrations of Den (5, 10, 20 μmol/L) for 24 h. Data are presented as mean ± SD. ***$p < 0.001$ *vs.* control group; #$p < 0.05$, ##$p < 0.01$ and ###$p < 0.001$ *vs.* H/R group. TNF: Tumor Necrosis Factor; IL: Interleukin; NLRP3: NOD-like Receptor Family Pyrin Domain Containing 3; ASC: Apoptosis-associated Speck-like protein containing a CARD; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase.

(Fig. 3B), suggesting the suppression of inflammation. These findings suggest that dendrobine can effectively alleviate the inflammation induced by H/R in cardiomyocytes.

3.4 Dendrobine activates the Nrf2/Keap1 signaling pathway in H9C2 cells under hypoxia/reoxygenation (H/R) conditions

Finally, we determined whether dendrobine could activate the Nrf2/Keap1 pathway in H/R-treated cells. H/R conditions caused a reduction in Nrf2 levels and Keap1 levels, suggesting suppression of the Nrf2/Keap1 pathway in H9C2 cells (Fig. 4). However, dendrobine treatment reversed these effects, with a dose-dependent rise in Nrf2 and Keap1 expression (Fig. 4). The activation of the Nrf2/Keap1 pathway induced by dendrobine is believed to play a significant role in providing protection to cardiomyocytes subjected to hypoxia/reoxygenation treatment.

4. Discussion

AMI remains a leading cause of mortality worldwide, despite advancements in treatment [8]. The urgency of developing effective drug therapies for AMI is underscored by the disease's complex pathology, which involves myocardial ischemia, oxidative stress, inflammation and apoptosis [9–11]. Apoptosis of cardiomyocytes and the presence of inflammation are significant factors contributing to the progression of cardiac remodeling, decline in cardiac function, and manifestation of heart failure symptoms in individuals suffering from AMI [12–14]. Given their critical roles in AMI, targeting these pathways is a rational and urgent strategy for developing novel therapeutic agents. Our study is grounded on the necessity for efficient intervention, exploring the capacity of dendrobine as a cardioprotective agent in the setting of AMI.

In this study, we employed an *in vitro* AMI model using H9C2 rat cardiomyocytes subjected to H/R conditions to mimic ischemia/reperfusion injury. This model enabled us to explore the impacts of dendrobine on crucial cellular mechanisms linked to AMI, including proliferation, apoptosis and inflammation [15]. Our findings indicate that dendrobine significantly promotes the proliferation of cardiomyocytes, inhibits apoptosis, and reduces inflammatory responses under H/R conditions. Therefore, dendrobine holds potential as a therapeutic agent for AMI, offering a rational approach to mitigating the deleterious effects of myocardial injury.

Dendrobine, a sesquiterpene alkaloid isolated from Dendrobium, has been shown to possess a variety of biological activities [7, 16]. Neuroprotection, anti-inflammatory, and anti-apoptotic effects are among its main functions [6, 17, 18]. Dendrobine has demonstrated efficacy in reducing cognitive dysfunction in diabetic encephalopathy, attenuating osteoclast differentiation, and protecting dopaminergic neurons in *Parkinson*'s disease models [5, 19]. Additionally, it demonstrates anti-cancer characteristics through the inhibition of cancer cell migration and metastasis [20]. Given its ability to modulate these critical cellular processes, particularly inflammation and apoptosis, dendrobine's potential impact on cardiovascular diseases, including AMI, is of significant interest. Our study contributes additional proof to endorse the cardioprotective benefits of dendrobine in the setting of AMI through its regulation of cell proliferation, apoptosis and inflammation.

Dendrobine's therapeutic effects in various diseases are mediated through different molecular mechanisms and signaling pathways. For instance, it has been demonstrated to block ferroptosis by regulating the Nrf2/Glutathione Peroxidase 4 (GPX4) axis in diabetic encephalopathy, modulate the Reactive Oxygen Species (ROS)/Nuclear Factor of Activated T-cells, Cytoplasmic 1 (NFATc1)/Matrix Metalloproteinase-9 (MMP9) cascade in inflammatory bone degradation and alleviate Endoplasmic Reticulum (ER) stress in Parkinson's disease [5]. In contrast, our research highlights the role of dendrobine in activating the Nrf2/Keap1 signaling pathway,

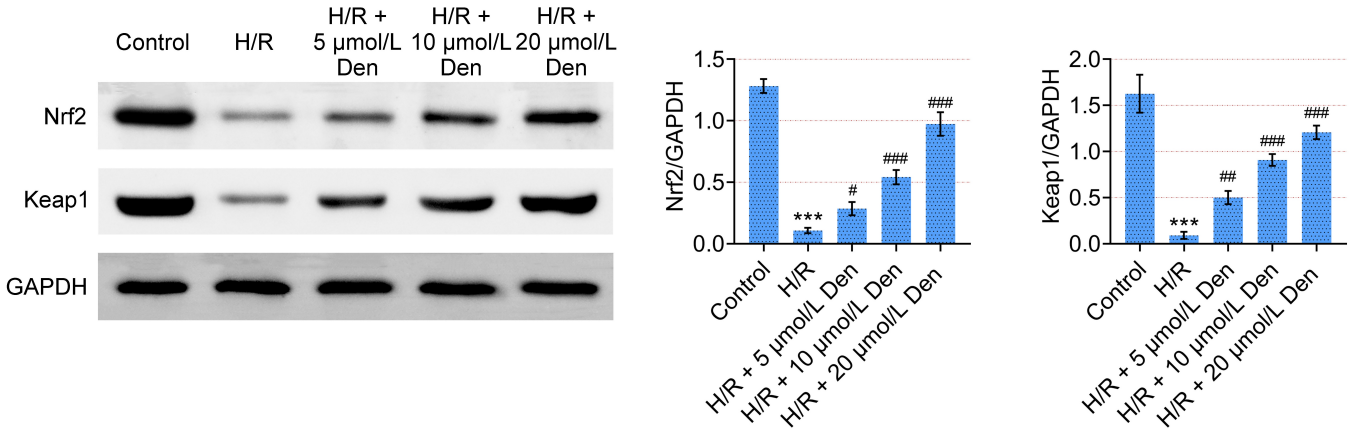

FIGURE 4. Dendrobine (Den) activates the Nrf2/Keap1 signaling pathway in H9C2 cells under hypoxia/reoxygenation (H/R) conditions. Immunoblot analysis of Nrf2 and Keap1 protein expression in H9C2 cells treated with H/R alone or in combination with various concentrations of Den (5, 10, 20 μmol/L). The expression levels of Nrf2 and Keap1 were normalized to GAPDH and quantified. Data are presented as mean ± SD. ***$p < 0.001$ *vs.* control group; #$p < 0.05$, ##$p < 0.01$ and ###$p < 0.001$ *vs.* H/R group. Nrf2: Nuclear factor erythroid 2-related factor 2; Keap1: Kelch-like ECH-associated protein 1; GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase.

which is central to its cardioprotective effects in AMI. Through a comparison of these results, we can acknowledge the wide range of biological effects exhibited by dendrobine and its capacity to impact different disease pathways through unique mechanisms.

The Nrf2/Keap1 pathway is a critical regulator of cellular responses to oxidative stress and inflammation. The activation of Nrf2 results in the upregulation of genes responsible for antioxidants and cytoprotection, thereby shielding cells from oxidative harm and decreasing inflammation. In cardiovascular diseases, particularly AMI, the Nrf2/Keap1 pathway plays a pivotal role in mitigating myocardial injury by inhibiting apoptosis and inflammation [21]. Keap1-Nrf2-Antioxidant Response Element (ARE) can be separated into two components, with one located in the cytoplasm and the other in the nucleus. Normally, Keap1 binds to Nrf2 in the cytoplasm, which is in an inactive state and if it is not activated, Nrf2 will be ubiquitinated and then degraded [21]. If stimulated, the interaction between Keap1 and Nrf2 becomes labile, leading to the release of Nrf2. Nrf2 is released (to start a new mission), transferred to the nucleus and bound to ARE, activate the transcription of downstream genes. This activates the translation of a cascade of associated proteins, ultimately enabling them to carry out various physiological functions [21]. Therefore, we believe that dendrobium may affect AMI by activating Keap1, leading to the release of Nrf2 into the nucleus and activating downstream gene transcription.

Compared with the current treatment methods, Traditional Chinese Medicine (TCM) treatment still has a long way to go. More investigations into the mechanisms are necessary to identify viable targets, while ensuring better management of the drug's toxicity. Subsequent studies should be combined with multi-omics methods and validated at animal and clinical levels. Our study demonstrates that dendrobine enhances the activation of this pathway in H9C2 cardiomyocytes under H/R conditions, suggesting that its cardioprotective effects are, at least in part, mediated through the modulation of Nrf2/Keap1 signaling. This discovery highlights the healing possibilities of focusing on this pathway in addressing AMI.

Despite the promising results of our study, there are limitations that should be acknowledged. This study is limited by the rudimentary design of a cellular model for AMI, falling within the scope of cellular-level research. In the next step, we will focus on building an animal model of AMI to study the effects of dendrobium base on AMI animals and further clarify the molecular mechanism of dendrobium base's improvement of AMI by means of multi-omics analysis. Future studies should prioritize confirming these results using animal models and delving into the specific mechanisms responsible for dendrobine's cardioprotective effects.

5. Conclusions

In summary, our study provides evidence that dendrobine exerts significant cardioprotective effects in an *in vitro* model of AMI by promoting cardiomyocyte proliferation, inhibiting apoptosis, reducing inflammation and activating the Nrf2/Keap1 signaling pathway. The results indicate that dendrobine has the potential to be a valuable therapeutic option for AMI, providing fresh perspectives on the advancement of efficacious remedies for this critical medical situation.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

QL, LL—designed the study and carried them out; prepared the manuscript for publication and reviewed the draft of the manuscript. QL, LL, SDC, PLJ—supervised the data collection; analyzed the data; interpreted the data. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This article does not contain any studies with human participants or animals performed by any of the authors.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Qian Liu, Li Lin, Shudan Cao, Peilun Jin. Dendrobine promotes cardiomyocyte proliferation and inhibits apoptosis and inflammation in an *in vitro* acute myocardial infarction model. Signa Vitae. 2025; 21(5): 79-85. doi: 10.22514/sv.2025.069.