



## SIRT1 regulates hypoxia-induced oxidative stress in cardiomyocytes via PI3K/MTOR signaling

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### ABSTRACT

This work was developed to investigate the activation of silent information regulator 1 (SIRT1) to regulate hypoxia-induced oxidative stress in cardiomyocytes through the PI3K/MTOR signaling pathway. For this purpose, 30 SD healthy rats were selected, and 10 of them were randomly selected as the control group. The remaining 20 rats were established as acute myocardial infarction model rats, and randomly divided into model group and activated SIRT1 group. Interventions were performed on rats in each of the 3 groups. ROS staining, inflammatory factors [IL-6, IL-1 $\beta$  levels], H9c2 cell viability, Caspase3 and Caspase8 activity, antioxidant enzyme indexes [SOD, CAT, MDA levels], SIRT1, PI3K, MTOR, HIF-1 $\alpha$ , HO-1, GLUT1 mRNA expression were compared between groups. Results showed that IL-6 and IL-1 $\beta$  levels were abnormally elevated in the model group compared with the control group ( $P < 0.05$ ). IL-6 and IL-1 $\beta$  levels decreased in the activated SIRT1 group compared with the model group ( $P < 0.05$ ). H9c2 cell viability decreased and Caspase3 and Caspase8 activities increased in the model group compared with the control group ( $P < 0.05$ ). H9c2 cell viability increased and Caspase3 and Caspase8 activities decreased in the activated SIRT1 group compared with the model group ( $P < 0.05$ ). SOD and CAT levels were abnormally decreased and MDA levels were abnormally increased in the model group compared with the control group ( $P < 0.05$ ). SOD and CAT levels were abnormally increased and MDA levels were decreased in the activated SIRT1 group compared with the model group ( $P < 0.05$ ). PI3K and SIRT1 expression decreased and MTOR expression increased in the model group compared with the control group ( $P < 0.05$ ). PI3K and SIRT1 expression increased and MTOR expression decreased in the activated SIRT1 group compared with the model group ( $P < 0.05$ ). The expression of HIF-1 $\alpha$ , HO-1 and GLUT1 mRNA increased in the model group compared with the control group, and the difference was statistically significant ( $P < 0.05$ ). The expression of HIF-1 $\alpha$ , HO-1, and GLUT1 mRNA decreased in the activated SIRT1 group compared with the model group, and the difference was statistically significant ( $P < 0.05$ ). It was concluded that the activation of SIRT1 can regulate PI3K/MTOR signaling pathway, thus reducing hypoxia-induced oxidative stress in cardiomyocytes, inflammatory conditions and enhancing cardiomyocyte viability, with better intervention effects.

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### Introduction

Myocardial infarction is a serious threat to human life and health. Its incidence, as well as death rate, occupies the first place among various cardiovascular diseases (1-2). Myocardial infarction is a clinical disease caused by the occlusion of coronary arteries, which results in myocardial cell necrosis due to severe local myocardial ischemia and hypoxia (3-4). Clinical studies have known that oxidative damage, apoptosis, and necrosis of cardiomyocytes are key factors in the recovery of cardiac function after clinical treatment of myocardial infarction, so antioxidant therapy and

inhibition of myocardial apoptosis are important for the prevention and control of ischemic heart disease such as myocardial infarction (5). SIRT1 is a silent information regulator 1, which is expressed in several organs of the body, such as the brain, heart, and adipose tissue. It mainly survives in the nucleus and has a regulatory role in various signaling pathways in the organism (6-7). In this study, SIRT1 was regulated in hypoxia-induced cardiomyocytes, aiming to investigate the effect of SIRT1 in regulating hypoxia-induced oxidative stress in cardiomyocytes via the PI3K/MTOR signaling pathway.

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## Materials and methods

### Materials, sampling

30 healthy rats were selected and provided by Spelford (Beijing) Biotechnology Co. The rats were aged 9 to 12 months, with a mean age of (10.5±1.2) months. The body weight of rats ranged from 221 to 247 g, with a mean weight of (234.1±10.9) g. The rats were kept for 1 week at 45%-50% relative humidity and temperature (24.1±2.3) °C and 12h light was maintained with alternating day and night illumination. The heart tissue was then extracted by opening the chest under aseptic conditions, placed in trypsin and gently blown several times, and the above steps were repeated 3 to 5 times until the tissue block was completely digested and whitened in color. The digested filtered liquid was collected and processed by centrifugation at 1000/min for 5 min and the supernatant was discarded. The cell clusters obtained by centrifugation were diluted with DMEM solution into cell suspensions in culture flasks, purified by differential appanation method and counted by Trypan Blue for cell viability. The cell suspensions were prepared at a concentration of 5x10<sup>6</sup>/L and inoculated in 5-well culture plates. The plates were incubated at 37 °C in a 50 mL/L CO incubator for 24 h. The culture medium was changed and the cell morphology was observed.

### Modeling

Myocardial H9c2 cells of appropriate density were inoculated for modeling. Control group: myocardial H9c2 cells were cultured normally at 37 °C in a 5% CO<sub>2</sub> incubator. Hypoxic group: myocardial H9c2 cells were cultured under 95% N<sub>2</sub>+4% CO<sub>2</sub>+1% O<sub>2</sub> conditions. Activation of SIRT1 group: transfection of pdDNA3. 1-SIRT1 was performed after modeling.

### DHE staining

The production of intracellular reactive oxygen species ROS was detected using the fluorescent probe dihydroethidium (DHE). Cardiomyocytes were placed inside a 6-well plate, then washed with PBS solution and incubated in 5 μmol/L DHE for 30 min. The cells were then washed again with PBS, and the cardiomyocyte ROS content was observed in an inverted fluorescence microscope.

### Cell viability, Caspase activity assay

Cell viability was evaluated using the MMT method. The formula was calculated as cell viability (%) = (A<sub>treatment group</sub> - A<sub>blank group</sub>)/(A<sub>control group</sub> - A<sub>blank group</sub>) × 100%. Caspase activity was assayed using cytosolic lysate, and the assay was performed in strict accordance with the reagent instructions.

### Inflammatory factors, antioxidant enzyme index assay

IL-6, IL-1β, SOD, CAT and MDA levels were measured using ELISA. The enzyme plates were labeled at room temperature. Standards were prepared and samples were diluted at a ratio of 1:2. The serum was to be tested and the standard was added to the kit at 100 μl per well and incubated for 2h in a 37 °C thermostat. Reaction plates were washed repeatedly. Antibody working solution was added at 1:100 for 100 μl per well and incubated for 45 min at secondary temperature. Reaction plates were washed again. 100 μl of IL-6, IL-1β, SOD, CAT and MDA solutions were added to each well and incubated again for 45 min. 100 μl of termination solution was added to each well to terminate the reaction. The absorbance was measured at 450 nm. The level of the indicator to be measured was proportional to the shade of the color response. The level of the factor to be measured was calculated.

### PI3K, MTOR expression

PI3K, MTOR expression was detected by Western blot. Specimens to be tested were rinsed in PBS buffer and lysed for 30 min. After adding protein buffer and electrophoresis treatment for 10 min, the electrotransformed membrane was soaked in 10% milk and incubated for 1 day under a closed environment at room temperature. After removal and rinsing with TBST solution, the secondary antibody was conjugated, washed and color developed after 60 min. Cellular PI3K and MTOR expression were examined.

### SIRT1 expression

SIRT1, HIF-1α, HO-1 and GLUT1 mRNA expression was detected using RT-PCR. Total RNA from the cells to be tested was extracted and assayed for purity and content. cDNA was obtained by reverse transcription processing. Primers were designed using

Primer 5. 0 software and calculated using the  $2^{-\Delta\Delta Ct}$  method with an internal reference of U6. The reverse transcription reaction conditions were set to 25 °C for 10 min, 40 °C for 60 min, and 85 °C for 5 min. The amplification conditions were set to 94 °C for 20s, 72 °C for 30s and 60 °C for 30s. Thirty-five cycles were performed. The expression of HIF-1 $\alpha$ , HO-1, GLUT1 mRNA and SIRT1 to be detected was calculated using the  $2^{-\Delta\Delta Ct}$  method.

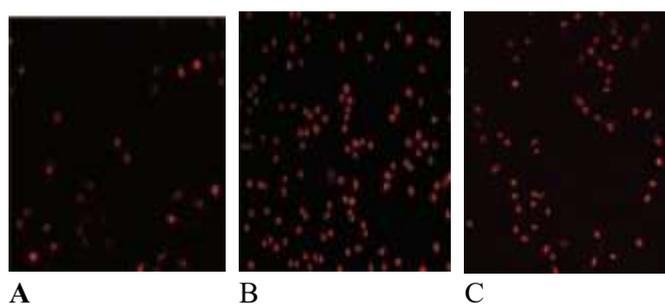
### Statistical processing

SPSS 21. 0 software was used for analysis. The measurement data were described using the mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ). An independent t-test was used for two-by-two comparisons between groups. Multiple intergroup comparisons were calculated using F-values, and P-values  $< 0.05$  were considered statistically significant.

## Results and discussion

### DHE staining

As shown in Figure 1A, DHE staining of the control group, showed a low number of reactive oxygen ROS cell nuclei and red fluorescence. Figure 1B shows the DHE staining of the model group, showing an increase in the number of reactive oxygen ROS cell nuclei. Figure 1C shows the activated SIRT1 group, showing a decrease in the number of reactive oxygen ROS cell nuclei.

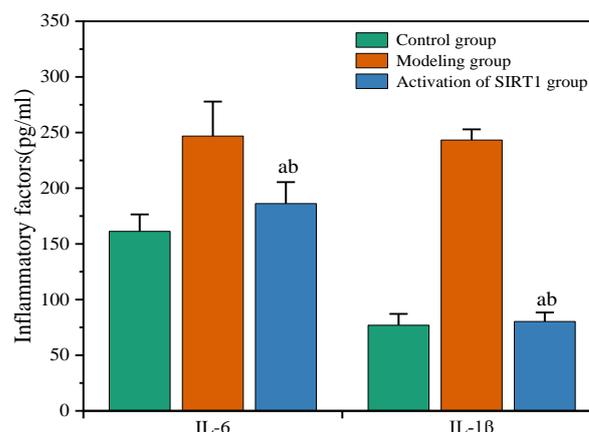


**Figure 1.** Staining of reactive oxygen ROS cells in each group. A: DHE staining of the control group, B: DHE staining of the model group and C: Activated SIRT1 group

### Comparison of inflammatory factors

As shown in Figure 2, the levels of IL-6 and IL-1 $\beta$  were abnormally increased in the model group compared with the control group, and the differences were all statistically significant ( $P < 0.05$ ). The levels of IL-6 and IL-1 $\beta$  decreased in the activated SIRT1

group compared with the model group, and the differences were statistically significant ( $P < 0.05$ ).



**Figure 2.** the levels of IL-6 and IL-1 $\beta$  in each group Note: Compared with the control group, <sup>a</sup> $P < 0.05$ ; compared with the model group, <sup>b</sup> $P < 0.05$ .

### Comparison of H9c2 cell viability, Caspase3 and Caspase8 activities among groups

As shown in Table 2, H9c2 cell viability decreased and Caspase3 and Caspase8 activities increased in the model group compared with the control group, and the differences were statistically significant ( $P < 0.05$ ). H9c2 cells increased and Caspase3 and Caspase8 activities decreased in the activated SIRT1 group, and the differences were statistically significant ( $P < 0.05$ ). Compared with the model group, H9c2 cell viability increased and Caspase3 and Caspase8 activities decreased in the activated SIRT1 group, with statistically significant differences ( $P < 0.05$ ).

**Table 2.** Comparison of H9c2 cell viability, Caspase3 and Caspase8 activities among groups ( $\bar{x} \pm s$ )

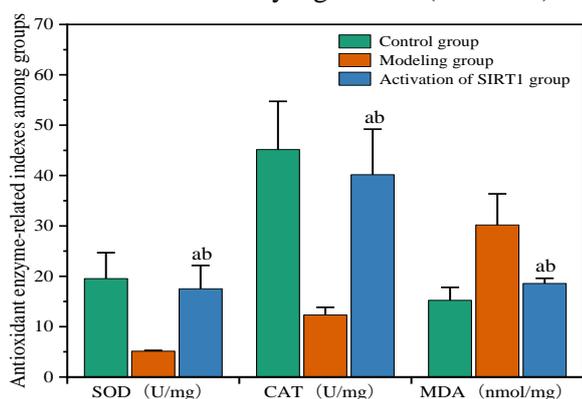
Group	H9c2cell viability (%)	Caspase3 (mmol/mg)	Caspase8 (mmol/mg)
Control group	96.58 $\pm$ 16.35	3.26 $\pm$ 0.27	8.12 $\pm$ 0.71
Modeling group	60.23 $\pm$ 6.53	7.86 $\pm$ 1.63	13.26 $\pm$ 2.64
Activation of SIRT1 group	91.26 $\pm$ 12.06 <sup>ab</sup>	3.99 $\pm$ 0.19 <sup>ab</sup>	9.16 $\pm$ 0.89 <sup>ab</sup>

Note: Compared with the control group, <sup>a</sup> $P < 0.05$ ; compared with the model group, <sup>b</sup> $P < 0.05$ .

### Comparison of antioxidant enzyme-related indexes among groups

As shown in Figure 3, compared with the control group, SOD and CAT levels abnormally decreased and MDA levels abnormally increased in the model group, and the difference was statistically significant ( $P < 0.05$ ). Compared with the model group, SOD and CAT levels abnormally increased and MDA

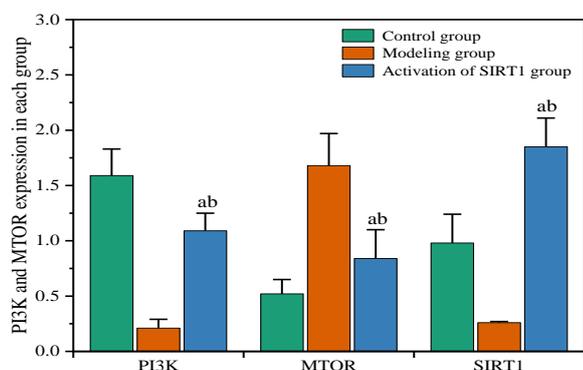
levels decreased in the activated SIRT1 group, and the difference was statistically significant ( $P < 0.05$ ).



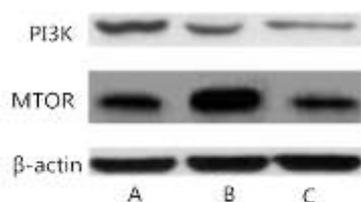
**Figure 3.** SOD, CAT and MDA amounts in different groups. Note: Compared with the control group, <sup>a</sup> $P < 0.05$ ; compared with the model group, <sup>b</sup> $P < 0.05$ .

### Comparison of SIRT1, PI3K and MTOR expression

As shown in Figures 4 and 5, compared with the control group, PI3K and SIRT1 expression decreased and MTOR expression increased in the model group, and the differences were statistically significant ( $P < 0.05$ ). Compared with the model group, PI3K and SIRT1 expression increased and MTOR expression decreased in the activated SIRT1 group, and the differences were statistically significant ( $P < 0.05$ ).



**Figure 4.** Expression changes of PI3K, MTOR and SIRT1 in different groups. Note: Compared with the control group, <sup>a</sup> $P < 0.05$ ; compared with the model group, <sup>b</sup> $P < 0.05$ .



**Figure 5.** PI3K, MTOR expression in Western Blotting map

### Comparison of HIF-1 $\alpha$ , HO-1 and GLUT1 mRNA expression

As shown in Table 3, the expression of HIF-1 $\alpha$ , HO-1, and GLUT1 mRNA increased in the model group compared with the control group, and the difference was statistically significant ( $P < 0.05$ ). Compared with the model group, HIF-1 $\alpha$ , HO-1 and GLUT1 mRNA expression decreased in the activated SIRT1 group, and the difference was statistically significant ( $P < 0.05$ ).

**Table 3.** Comparison of HIF-1 $\alpha$ , HO-1 and GLUT1 mRNA expression

Group	HIF-1 $\alpha$	HO-1	GLUT1
Control group	0.00 $\pm$ 0.00	0.02 $\pm$ 0.01	0.02 $\pm$ 0.00
Modeling group	0.10 $\pm$ 0.01	0.13 $\pm$ 0.04	0.45 $\pm$ 0.16
Activation of SIRT1 group	0.01 $\pm$ 0.01 <sup>ab</sup>	0.06 $\pm$ 0.01 <sup>ab</sup>	0.10 $\pm$ 0.03 <sup>ab</sup>

Note: Compared with the control group, <sup>a</sup> $P < 0.05$ ; compared with the model group, <sup>b</sup> $P < 0.05$ .

Myocardial cell oxidative damage, necrosis, and apoptosis are involved in the development process of ischemic heart disease, which includes coronary artery disease, myocardial infarction, and angina pectoris (8). Therefore, minimizing oxidative stress and inhibiting myocardial apoptosis have emerged as potential strategies for the current treatment of heart disease. Clinical studies have shown that SIRT1 and PI3K/MTOR signaling pathways are closely related and that their modulation enhances antioxidant capacity, reduces oxidative damage, and increases cell viability, thereby protecting cardiomyocytes from hypoxic damage (9-10).

It has been pointed out that during myocardial hypoxia, IL-1 $\beta$  is able to promote apoptosis of ischemic cardiomyocytes and also directly activate neutrophils, as well as cause damage to cardiomyocytes by blocking microvessels and releasing oxygen free radicals, thus exacerbating the injury process (11). IL-6, a chronic inflammatory mediator, is clinically produced in the regulation of the inflammatory response (12). In this study, it was shown that inflammation-related factors were abnormally increased in the model group, indicating a certain inflammatory response during oxidative stress in cardiac myocytes caused by hypoxia. The activation of SIRT1 to intervene in cardiomyocytes resulted in a decrease in the level of inflammatory factors, indicating that SIRT1 can regulate the

PI3K/MTOR signaling pathway and play a role in suppressing the inflammatory response.

Apoptosis is a regulatory mechanism for homeostatic regulation and organ development in tissue cells, and it has an important role in the process of myocardial infarction. Therefore, it can be concluded that myocardial apoptosis plays an important role in myocardial injury as a fundamental pathological change (13-14). Caspase3 and Caspase8 are factors commonly used clinically to detect apoptosis, and their detection provides a better evaluation of apoptosis (15). In this study, we found that Caspase3 and Caspase8 activities were abnormally increased in the model group, and this result indicates that the abnormal increase of Caspase3 and Caspase8 activities can lead to apoptosis of cardiomyocytes. Intervention with activated SIRT1 resulted in a decrease in Caspase3 and Caspase8 activity, indicating that SIRT1 can regulate the PI3K/MTOR signaling pathway and play a role in inhibiting apoptosis.

Clinical studies have shown that oxidative stress is closely related to myocardial cell injury and that it is an important factor in the development of ischemic heart disease. Clinical studies have demonstrated that oxidative stress includes an increase in the production of oxidative products and a decrease in the activity of antioxidant enzymes (16-17). Under normal circumstances, myocardial injury can be caused by ROS. When ROS are produced in the body, they can be cleared when the quantity is small. Conversely, when there are too much ROS, the body cannot clear them in time, and they will interact with deoxyribonucleic acid, lipids and proteins, leading to peroxidative damage in the body. Therefore, the timely and effective intervention of oxidative stress is important to reduce myocardial injury. In addition, some studies suggest that increased CAT and SOD activities in the organism can effectively inhibit MDA production and ROS production (18-19). The results of this paper showed that SOD and CAT levels decreased abnormally and MDA levels increased abnormally in the model group, and the intervention with activated SIRT1 increased SOD and CAT levels and decreased MDA levels. This result indicates that the intervention of cardiomyocytes using activated SIRT1 can improve the scavenging ability of oxygen free radicals in patients and has a better protective

effect on hypoxic cardiomyocytes.

SIRT1, a protein deacetylase, is capable of transferring the N-terminal acetyl group of DNA histone lysine and regulating the transcription process, as well as participating in cellular proliferation, apoptosis, and oxidative stress. Numerous clinical studies have shown that the PI3K/MTOR signaling pathway can regulate energy metabolism as well as promote angiogenesis, thereby enhancing the anti-hypoxic energy of cardiomyocytes (20-22). By stimulating the PI3K/MTOR signaling pathway, it can also inhibit coronary spasms, thus serving to reduce ischemia-induced cardiomyocyte injury. In this study, we show that activation of SIRT1 can regulate the PI3K/MTOR signaling pathway, which has the effect of mitigating oxidative stress in cardiomyocytes caused by hypoxia (23).

In summary, the activation of SIRT1 can regulate the PI3K/MTOR signaling pathway, thus reducing the cellular inflammatory response, oxidative stress and having a better protective effect on hypoxia-induced cardiomyocytes.

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None.

#### Conflict interest

The authors declare no conflict of interest.

#### References

1. Hussain S, Jamal SZ, Qadir F. Medication Adherence In Post Myocardial Infarction Patients. *J Ayub Med Coll Abbottabad*. 2018;30(4):552-557.
2. Skattebu J, Edvardsen T, Otterstad JE, et al. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: A systematic review and meta-analysis. *Eur J Prev Cardiol*. 2017;24(14):1555-1566.
3. Cider Å, Hambraeus K, Börjesson M, et al. Increased Physical Activity Post-Myocardial Infarction Is Related to Reduced Mortality: Results From the SWEDEHEART Registry. *J Am Heart Assoc*. 2018 ;7(24):e010108.
4. Driessen HE, van Veen TAB, Boink GJJ, et al. Emerging molecular therapies targeting myocardial infarction-related arrhythmias. *Europace*. 2017;19(4):518-528.
5. Arslanian-Engoren C, Bolger AF, Beltrame JF; American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and

- Prevention; and Council on Quality of Care and Outcomes Research. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2019;139(18):e891-e908.
6. Wang K, Qin YW, Zhao XX, et al. MiR-34a promotes myocardial infarction in rats by inhibiting the activity of SIRT1. *Eur Rev Med Pharmacol Sci*. 2019 ;23(16):7059-7065.
  7. Celikten M, Bacaksiz A, Kilic U. Premature Myocardial Infarction: Genetic Variations in SIRT1 Affect Disease Susceptibility. *Cardiol Res Pract*. 2019;2019:8921806.
  8. Liu Z, Ge J, Shi B, et al. Exosomal circHIPK3 Released from Hypoxia-Pretreated Cardiomyocytes Regulates Oxidative Damage in Cardiac Microvascular Endothelial Cells via the miR-29a/IGF-1 Pathway. *Oxid Med Cell Longev*. 2019;2019:7954657.
  9. Tian C, Chen X, Liu SM. Myocyte enhancer factor 2A delays vascular endothelial cell senescence by activating the PI3K/p-Akt/SIRT1 pathway. *Aging (Albany NY)*. 2019 ;11(11):3768-3784.
  10. Day CH, Mahalakshmi B, Huang CY, et al. Swimming exercise stimulates IGF1/ PI3K/Akt and AMPK/SIRT1/PGC1 $\alpha$  survival signaling to suppress apoptosis and inflammation in aging hippocampus. *Aging (Albany NY)*. 2020;12(8):6852-6864.
  11. Farhud D, Hescheler J, Nayernia K. Inflammatory Microenvironment of Acute Myocardial Infarction Prevents Regeneration of Heart with Stem Cells Therapy. *Cell Physiol Biochem*. 2019;53(5):887-909.
  12. Shou BY, Xie XX, Liu RH, et al. Latifolin protects against myocardial infarction by alleviating myocardial inflammatory via the HIF-1 $\alpha$ /NF- $\kappa$ B/IL-6 pathway. *Pharm Biol*. 2020;58(1):1156-1166.
  13. Wei L, Zhou Q, Tian H, Su Y, Fu GH, Sun T. Integrin  $\beta$ 3 promotes cardiomyocyte proliferation and attenuates hypoxia-induced apoptosis via regulating the PTEN/Akt/mTOR and ERK1/2 pathways. *Int J Biol Sci*. 2020;16(4):644-654.
  14. Qian L, Shen Y, Yu Y. CRTH2 promotes endoplasmic reticulum stress-induced cardiomyocyte apoptosis through m-calpain. *EMBO Mol Med*. 2018;10(3):e8237.
  15. Wang C, Zhang J, Zhao J, et al. Lens-specific deletion of the Msx2 gene increased apoptosis by enhancing the caspase-3/caspase-8 signaling pathway. *J Int Med Res*. 2018;46(7):2843-2855.
  16. Law BA, Liao X, Moore KS, Southard A, Roddy P, Ji R, Szulc Z, Bielawska A, Schulze PC, Cowart LA. Lipotoxic very-long-chain ceramides cause mitochondrial dysfunction, oxidative stress, and cell death in cardiomyocytes. *FASEB J*. 2018;32(3):1403-1416.
  17. Lei Q, Yi T, Chen C, et al. NF- $\kappa$ B-Gasdermin D (GSDMD) Axis Couples Oxidative Stress and NACHT, LRR and PYD Domains-Containing Protein 3 (NLRP3) Inflammasome-Mediated Cardiomyocyte Pyroptosis Following Myocardial Infarction. *Med Sci Monit*. 2018 30;24:6044-6052.
  18. Yang S, Xu H, Xing J. Protective effect of tanshinone IIA on H<sub>2</sub>O<sub>2</sub>-induced oxidative stress injury in rat cardiomyocytes by activating Nrf2 pathway. *J Recept Signal Transduct Res*. 2020;40(3):264-272.
  19. Shu L, Zhang W, Liang Z. Prokineticin 2 relieves hypoxia/reoxygenation-induced injury through activation of Akt/mTOR pathway in H9c2 cardiomyocytes. *Artif Cells Nanomed Biotechnol*. 2020;48(1):345-352.
  20. Zhang S, Zhao Y. Lentianan protects cardiomyocytes against hypoxia-induced injury by regulation of microRNA-22/Sirt1. *Artif Cells Nanomed Biotechnol*. 2019;47(1):3938-3946.
  21. Bakhshi, B. Heat and Drought Stress Response and Related Management Strategies in Oilseed Rape. *Agrotech Ind Crops* 2021; 1(4): 170-181. doi: 10.22126/atic.2022.7239.1034
  22. Ma R, Tang F, Xiao Y, et al. Sirt1 promotes autophagy and inhibits apoptosis to protect cardiomyocytes from hypoxic stress. *Int J Mol Med*. 2019;43(5):2033-2043.
  23. Rahbar-Karbasdehi E, Rahbar-Karbasdehi F. Clinical challenges of stress cardiomyopathy during coronavirus 2019 epidemic. *Cellular, Molecular and Biomedical Reports*, 2021, 1(2):88-90. doi:10.55705/cnbr.2021.145790.1018.