Article

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Salvianolic Acid B Ameliorated Chemotherapeutic Injury of Cardiac Myocytes through the Nrf2/ARE Signaling Pathway

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Background: Cardiotoxicity has been corroborated to be the toxic influence of cisplatin (CDDP). Oxidative stress and cardiomyocyte apoptosis play a vital part in cardiotoxicity induced by CDDP. Salvianolic acid Salvianolic acid B (SalB) is a monomeric component of Salvia miltiorrhiza, which has antioxidant and anti-inflammatory influences. In this research, we explored the mechanism of SalB in cardiotoxicity induced by CDDP.

Method: 36 Wistar rats were separated into sham subgroup, CDDP (10 mg/kg) subgroup, CDDP (10 mg/kg) + SalB (1 µM) subgroup at random, CDDP (10 mg/kg) + SalB (5 µM) subgroup and CDDP (10 mg/kg) + SalB (10 µM) subgroup, Nicotinic Acid Riboside (NAR, 5 µM), with 6 rats in each subgroup. The cardiac function of rats in each subgroup was estimated by echocardiography, and hematoxylin-eosin (HE) staining and Masson staining corroborated the pathological changes of cardiac tissue. Biochemical kits were utilized for detecting the lactate dehydrogenase (LDH), creatine kinase (CK), interleukin-1β (IL-1β), IL-18, and caspase-1 concentrations in serum, superoxide dismutase (SOD), and malondialdehyde (MDA) in myocardial tissue, TdT-mediated dUTP Nick-End Labeling (TUNEL) staining, and flow cytometry were utilized for estimating the apoptosis level in myocardial tissue, western blot was used for estimating caspase-3, Bcl2-Associated X (Bax) levels in myocardial tissue and proteins levels related to Nuclear factor E2 related factor 2 (Nrf2) signal pathway.

Results: CDDP-induced cardiac dysfunction, myocardial injury, boosted LDH and CK levels in serum ($p < 0.05$), memorably increased oxidative stress level in myocardial tissue ($p < 0.05$), boosted inflammatory response ($p < 0.05$), boosted apoptosis rate of cardiomyocytes ($p < 0.05$), and declined the Nrf2, NAD(P)H quinone oxidoreductase 1 (NQO1), heme oxygenase 1 (HO-1) protein levels ($p < 0.05$). Interestingly, SalB remedy could alleviate the changes caused by CDDP in the above parameters, significantly decrease the level of myocardial oxidative stress and apoptosis ($p < 0.05$).

Conclusions: SalB ameliorates the injury of cardiomyocytes induced by chemotherapy through oxidative stress mediated by the Nrf2/antioxidant response element (ARE) signal pathway.

Keywords: cisplatin; salvianolic acid B; oxidative stress; Nrf2; cardiomyocytes

Introduction

It is estimated that in 2020, the global new tumor instances will be 19.3 million, and tumor-related deaths will be about 10 million. The global tumor burden is estimated to reach 28.4 million in 2040 [1]. Although significant progress has been made in tumor remedy, chemotherapy is still the remedy method for many tumor patients. Cisplatin (CDDP) is a commonly utilized chemotherapy drug in clinics, which is used to treat various types of tumors, including testicular, ovarian, bladder, lung, pancreatic, breast, esophageal, etc. [2–4]. However, side effects such as cardiotoxicity, nephrotoxicity, ototoxicity, and neurotoxicity caused by long-term use of CDDP have weakened the efficacy of CDDP [5]. Cardiac toxicity caused by CDDP mainly includes arrhythmia, atrioventricular block, supraventricular tachycardia, etc. [6–8]. However, the underlying mechanism of CDDP cardiotoxicity has yet to be fully elucidated. Research has pointed out that oxidative stress and cardiomyocyte apoptosis are closely related to CDDP-induced cardiotoxicity [9]. CDDP lessens the activity of antioxidant enzymes and the level of total glutathione in cardiac tissue, and decreases the mitochondrial membrane potential in cardiomyocytes ($\Delta\Psi$m) level while promoting the release of cytochrome c into the cytoplasmic matrix [10,11]. Therefore, we speculated that intervention of oxidative stress and cardiomyocyte apoptosis is an effective way to alleviate CDDP-induced cardiotoxicity.

Salvianolic acid B (SalB) is a water-soluble phenolic acid compound extracted from Salvia miltiorrhiza and is a representative monomer component of Salvia miltiorrhiza [12]. SalB has antioxidant, anti-inflammatory, and anti-fibrotic influences and can affect the heart, brain, liver, kidney, and intestine [13]. Research has demonstrated that

SalB can enhance mitochondrial dysfunction, lessen reactive oxygen species (ROS) production under oxidative stress, and lessen apoptosis index, thus alleviating oxidative stress-induced intestinal cell damage [14]. A previous study on the role of SalB in cardiac arrest corroborated that administering SalB at the early stage of cardiopulmonary resuscitation could lessen myocardial injury and apoptosis, thereby preventing myocardial dysfunction and reducing end-organ damage after cardiac arrest [15]. In addition, SalB can inhibit cardiomyocyte apoptosis induced by oxygen-glucose deprivation by regulating apoptosis-related factors [16]. However, the role of SalB on CDDP-induced cardiac injury and the underlying molecular mechanism has not been studied.

Nuclear factor E2 related factor 2 (Nrf2) is a key regulator of cellular antioxidant response. When cells are stimulated by oxidative stress, the modification of -SH subgroup in Keap1 promotes the release of Nrf2, translocates Nrf2 to the nucleus, binds with antioxidant response elements, and promotes the expression of endogenous antioxidant enzymes, such as NAD(P)H quinone oxidoreductase 1 (NQO1), superoxide dismutase (SOD), catalase, heme oxygenase 1 (HO-1), Glutamate cysteine ligase, Glutathione S-transferase [17]. Studies have exhibited that activation of the Nuclear factor E2 related factor 2/antioxidant response element (Nrf2/ARE) signaling pathway can enhance cardiomyocytes' antioxidant stress capacity and play a vital part in cardio protection [18]. However, whether SalB can affect CDDP-induced oxidative stress injury through Nrf2/ARE signaling remains unclear. In the present research, we revealed the mechanism of action of SalB in chemotherapy-induced cardiotoxicity.

Materials and Methods

Animal Experiments

Adult male Wistar rats (200–220 g) utilized in this research were purchased from Beijing Biotech Biomedical Technology Co., Ltd. (Beijing, China). Preoperative rearing environment: 12 h light/dark cycle; ambient temperature (23 ± 2) °C; (55 ± 5)% humidity; well ventilated; noiseless environment; food and water *ad libitum*; diet was prohibited for 12 h preoperatively, but water was not prohibited.

The dose and remedy time of CDDP and SalB refer to previous studies [19,20]. 36 rats were divided into sham subgroups according to random number table method: CDDP (10 mg/kg) subgroup, CDDP (10 mg/kg) + SalB (1 μM) subgroup, CDDP (10 mg/kg) + SalB (5 μM) subgroup and CDDP (10 mg/kg) + SalB (10 μM) subgroup, Nicotinic Acid Riboside (NAR, 20 μM) subgroup, with 6 rats in each subgroup. The sham subgroup received normal saline as the normal control subgroup. Cardiotoxicity was induced by intraperitoneal injection of CDDP on the 7th day of the experiment in the CDDP subgroup, once daily for 5 consecutive days. The rats in the SalB remedy subgroup were intraperitoneally injected with SalB for 7 days, and CDDP was injected intraperitoneally on the 7th day of the experiment. 24 h after receiving the last drug remedy, pentobarbital sodium (50 mg/kg) was injected intraperitoneally for anaesthesia, and blood was collected from the abdominal aorta. Then, they were excessively anesthetized to death with 5% pentobarbital sodium (100 mg/kg), and the heart tissue was removed. CDDP (15663-27-1) was purchased from MedChemexpress (Trenton, NJ, USA), SalB from Sigma (HPLC, SML0048, Purity 99.97%, St. Louis, MO, USA), and NAR from Shanghai Raw Liquid Biology (Merrill, M68276, Purity ≥99%, Shanghai, China).

Cardiac Function Detection

On the day before death, rats were anesthetized with isoflurane (2 mg/kg) and fixed on the workbench. Cardiac function was measured by transthoracic echocardiography (VisualSonics, Toronto, Canada). Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular internal dimension in diastole (LVIDd), and left ventricular internal dimension in systole (LVIDs) were assessed. Ejection fraction (EF) and fractional shortening (FS) were calculated. Calculation formula: EF = [(LVEDV – LVESV)/LVEDV] × 100%; FS = [(LVIDd – LVIDs)/LVIDd] × 100%.

HE Staining of Myocardial Tissue

Rat myocardial tissue was collected, fixed with 4% paraformaldehyde, dehydrated with gradient ethanol, transparent in xylene, then embedded in paraffin and cut into 4 μM paraffin section. Sections were routinely dewaxed to water, stained with hematoxylin and eosin (C0105S, Beijing Soleibao, Beijing, China), dehydrated with gradient ethanol, transparent with xylene, and sealed with neutral resin. Histopathological changes were corroborated under an optical microscope (DM3000, Leica Microsystems Co., Ltd., Wetzlar, Germany). The changes in myocardial tissue were observed under a microscope.

Masson Staining of Myocardial Tissue

The myocardial tissue of rats was collected and made into paraffin sections. It was routinely dewaxed to water and stained according to the instructions of Masson's three-color staining kit (G1346, Solarbio, Beijing, China) to observe the changes in collagen fibers in the myocardial tissue. The proportion of myocardial collagen volume fraction (CVF) was calculated using Metic Med 6.0 software (Bio-Rad, Hercules, CA, USA), CVF = collagen area/total area × 100%.

Biochemical Detection

According to the manufacturers' instructions, lactate dehydrogenase (LDH, TR20015), creatine kinase (CK, E-CK-A362), interleukin (IL)-1β (PI305), IL-18 (PI553),

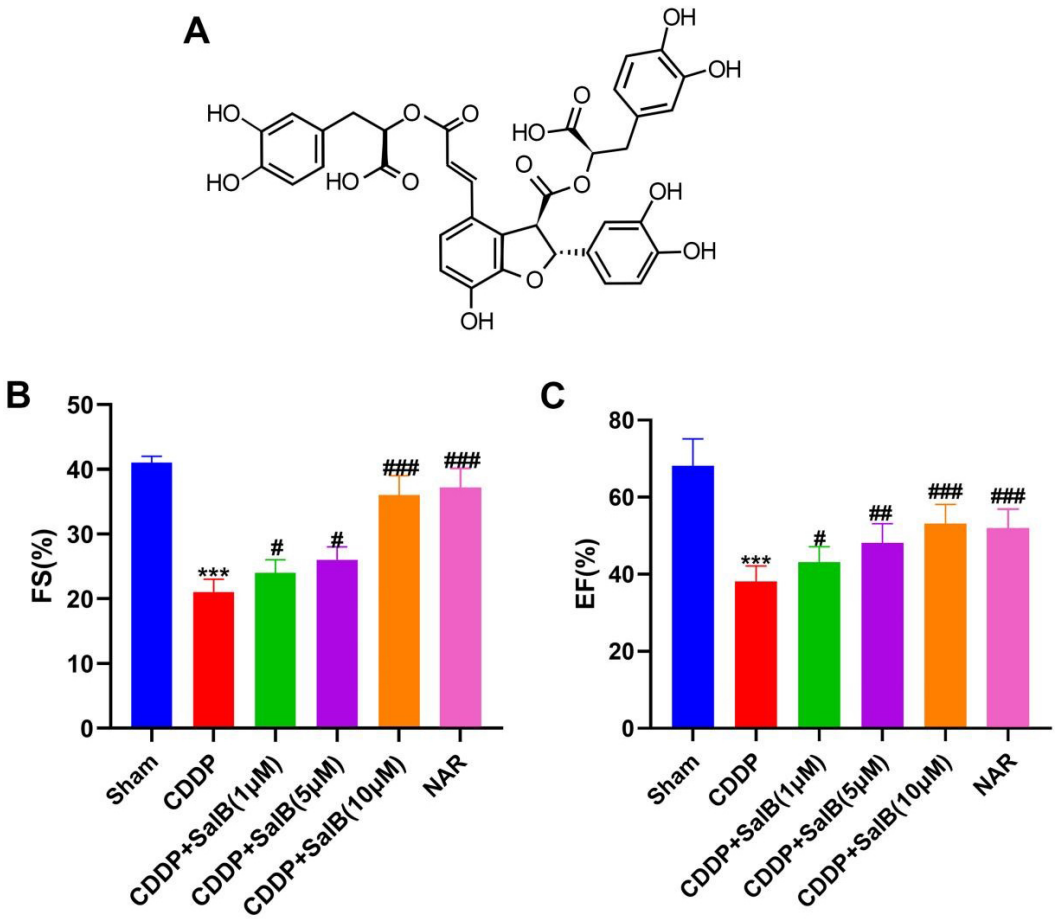

Fig. 1. SalB can restrain cisplatin (CDDP)-induced cardiac insufficiency. (A) Chemical structure of Salvianolic acid B (SalB). Echocardiography exhibited the influence of SalB on CDDP-induced cardiac insufficiency. (B) Fractional shortening (FS). (C) Ejection fraction (EF). Data presented as mean ± SD, n = 6, $^{***}p < 0.001$, contrasted to sham subgroup; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, compared to CDDP subgroup. NAR, Nicotinic Acid Riboside.

and caspase-1 (KTA3020) were estimated in rats' serum. All biochemical reagent kits were obtained from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). The contents of SOD activity (EIASODC) and malondialdehyde (MDA) in rat myocardial tissue were estimated.

TUNEL Staining

The paraffin tissue section specimen was taken and operated according to the instructions of the TdT-mediated dUTP Nick-End Labeling (TUNEL) apoptosis detection kit (C1091, Roche, Shanghai, China). Three slices were taken from each specimen, and five non-overlapping high-magnification fields of myocardial injury were randomly selected from each slice. TUNEL-positive cells were counted with Image-Pro plus image analysis software, and the apoptotic index (AI) was calculated: AI = number of apoptotic cells/total number of cells × 100%.

Flow Cytometry Detection

Rat cardiomyocytes were isolated, and the apoptotic rate of cardiomyocytes was estimated using an Annexin-V Fluorescein Isothiocyanate (FITC)/Propidium Iodide (PI) apoptosis detection kit (A111-01, HaiGene Biotech Co., Ltd., Harbin, China). Cells were collected resuspended in PBS, and 10 µL Annexin V-FITC and 10 µL PI, were gently mixed and incubated at 4 °C for 30 min in a dark place. Flow cytometry (BD Accuri™ C6, ThermoFisher Scientific, Waltham, MA, USA) for detection.

Western Blot

The total protein was extracted using RIPA buffer (89901, Beijing Soleibao, Beijing, China). After determining protein concentration, proteins were separated with 12% SDS polyacrylamide gel (SDS-PAGE) and transferred to PVDF membrane (3010040001, Millipore, Burlington, MA, USA). 5% skim milk powder was blocked overnight at 4 °C. The primary antibodies Caspase-3 (1:1000, ab32351, Abcam, Shanghai, China), Bcl2-Associated X (Bax) (1:1000, ab32503, Abcam, Shanghai, China), B-cell lymphoma-2 (Bcl-2, 1:1000, ab182858, Abcam, Shanghai, China) and tubulin (1:1000, ab7291, Abcam, Shanghai, China) were added and incubated for 1 h at room

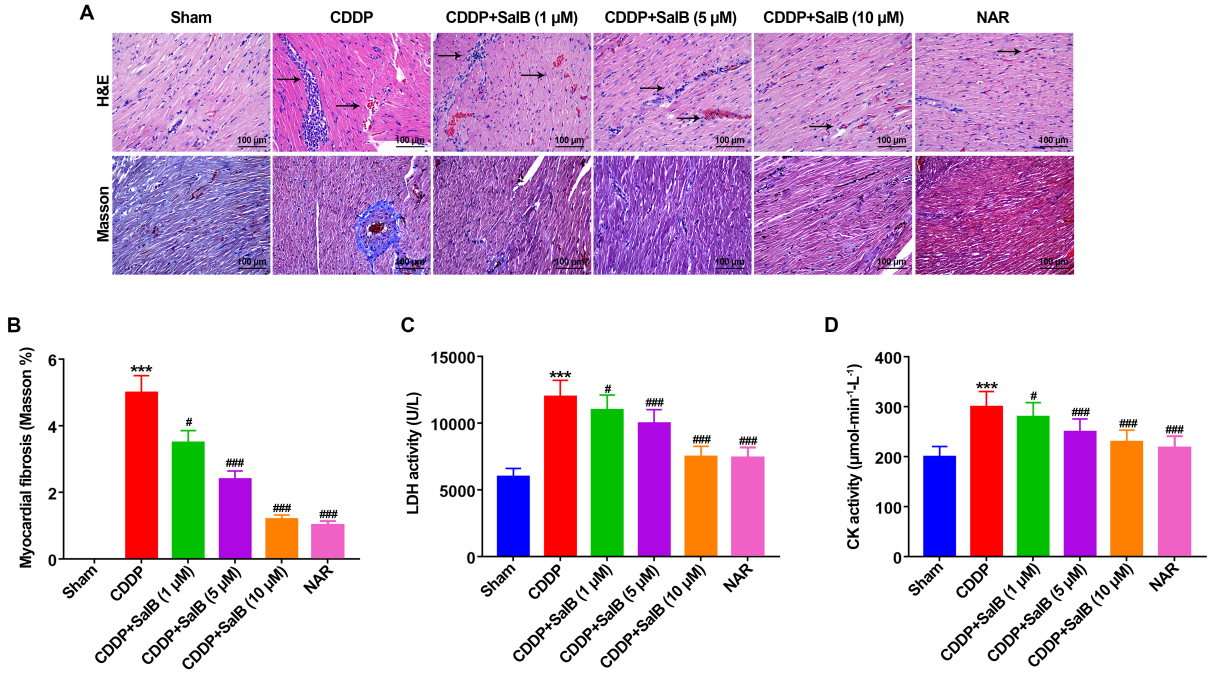

Fig. 2. SalB can alleviate CDDP-induced myocardial injury. (A) Hematoxylin-eosin (HE) staining results of rat myocardial tissue (scale bar: 100 μm. Magnification: ×200). Black arrows represented inflammatory infiltration. (B) Masson staining results of rat myocardial tissue. Changes of serum myocardial injury markers in rats. Comparison of serum (C) lactatedehydrogenase (LDH) and (D) Creatine Kinase (CK) activity. Data presented as mean ± SD, $^{***}p < 0.001$, contrasted to sham subgroup; $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$, compared to CDDP subgroup.

temperature. After washing the membrane, horseradish peroxidase-labeled goat anti-rabbit secondary antibody (1:2000, ab05718, Abcam, Shanghai, China) was added and incubated for 1 h at room temperature. ECL chemiluminescence reagent (34577, Millipore, Burlington, MA, USA) was used for color development, a gel imaging system was used for imaging, and ImageJ software (version number: ImageJ1, NIH, Bethesda, MA, USA) was used for grayscale analysis of images.

Statistical Analysis

SPSSv20.0 software (IBM, Amonk, NY, USA) was utilized for statistical analysis. The experimental data were all metrological data, expressed as mean ± standard deviation (mean ± SD). One-way ANOVA was utilized for comparison among the subgroups. Follow-up analyses were conducted using Tukey's post-hoc multiple comparison approach. $p < 0.05$ was statistically significant.

Results

SalB can Restrain CDDP-Induced Cardiac Insufficiency

Fig. 1A exhibited the structure of SalB. Firstly, we explored the cardioprotective influence of SalB on CDDP-induced cardiac insufficiency. The results showed that CDDP induced FS and EF reduction, while rats treated with SalB prevented CDDP-induced inhibition of FS and EF ($p < 0.05$, Fig. 1B,C). These results implied that SalB can restrain CDDP-induced cardiac insufficiency.

SalB can Lessen CDDP-Induced Myocardial Injury

We utilized hematoxylin-eosin (HE) and Masson staining to observe the pathological changes in rat myocardium. HE staining exhibited that the morphology and structure of cardiomyocytes in the sham subgroup were complete, and the fiber structure was arranged orderly and closely. CDDP-induced rat cardiomyocytes were irregular in shape, enlarged in cell space, necrotic, and broken in fiber structure. While the histological changes were lessened in the SalB remedy subgroup ($p < 0.05$, Fig. 2A). Masson staining exhibited that cardiomyocytes in the sham subgroup were arranged orderly. CDDP induced cardiac myocytes to be disordered, and a few collagen fibers stained positively. SalB remedy can restrain the degree of myocardial injury ($p < 0.05$, Fig. 2A,B). These results were consistent with serum LDH and CK concentrations. CDDP-induced rats exhibited elevated LDH and CK concentrations in serum, indicating myocardial injury, and this influence was reversed in SalB-treated rats ($p < 0.05$, Fig. 2C,D). These results suggested that SalB can attenuate CDDP-induced myocardial injury.

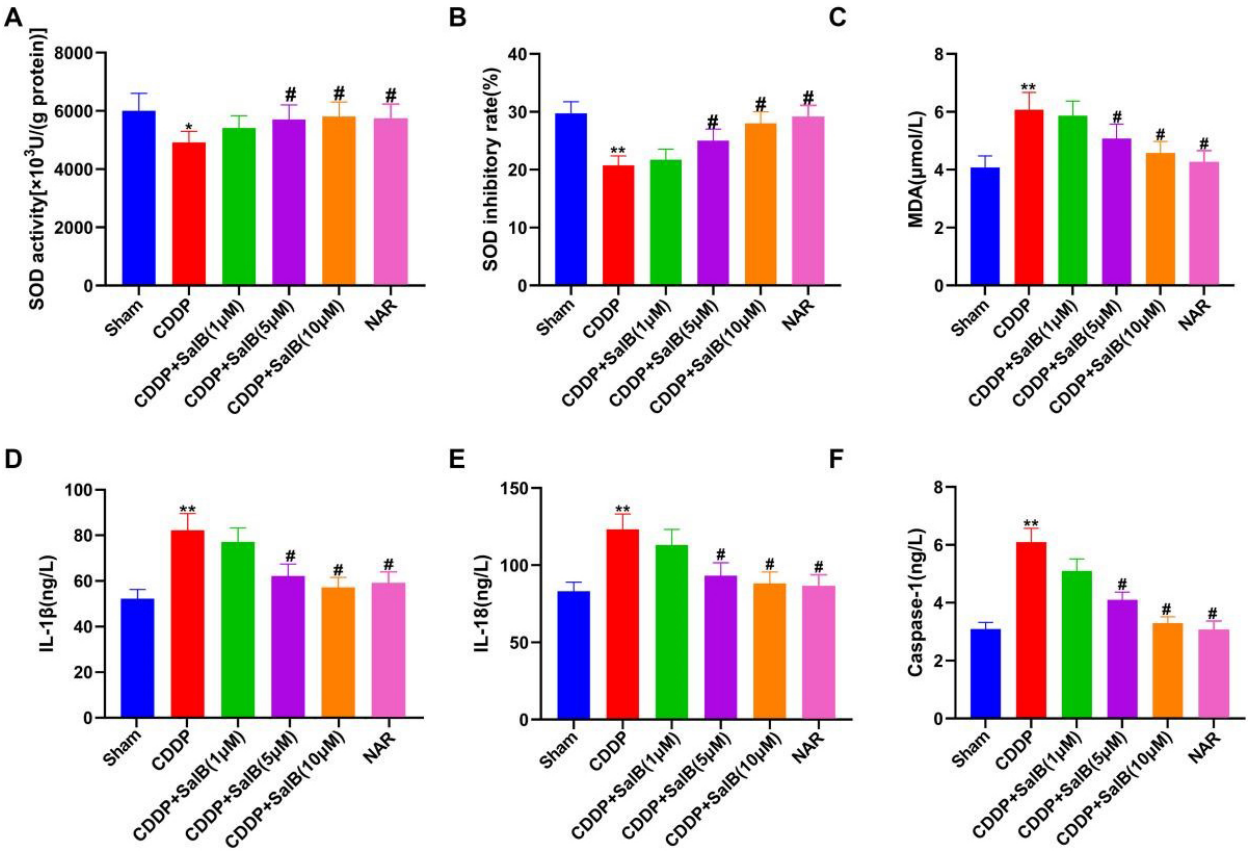

Fig. 3. SalB can lessen CDDP-induced oxidative stress and inflammatory damage. (A) Superoxide dismutase (SOD) activity and (B) inhibition rate and (C) malondialdehyde (MDA) content in myocardial tissue of rats. Rat serum (D) interleukin (IL)-1β (E) Comparison of IL-18 and (F) caspase-1 concentrations. Data presented as mean $\pm$ SD, $^{*}p < 0.05$, $^{**}p < 0.01$, compared to sham subgroup; $^{\#}p < 0.05$, compared to CDDP subgroup.

SalB can Lessen CDDP-Induced Oxidative Stress and Inflammatory Damage

To better understand the antioxidant and anti-inflammatory influences of SalB, we estimated the concentrations of SOD and MDA in rat myocardial tissue and IL-1β, IL-18, and caspase-1 in rat serum. It was corroborated that the activity and inhibition rate of SOD declined, and the MDA level increased in the myocardial tissue of rats induced by CDDP. However, SOD activity and inhibition rate were elevated, and MDA concentrations declined in the myocardium of rats pretreated with SalB ($p < 0.05$, Fig. 3A–C). Furthermore, our results showed that CDDP-induced IL-1β, IL-18, and caspase-1 concentrations were elevated in rat serum, while SalB remedy declined these inflammatory factors concentrations ($p < 0.05$, Fig. 3D–F). These data suggested that SalB can ameliorate CDDP-induced oxidative stress and inflammatory damage.

SalB can Lessen CDDP-Induced Cardiomyocyte Apoptosis

In addition, we estimated cardiomyocyte apoptosis by TUNEL staining and flow cytometry. The results demonstrated that CDDP induction significantly increased the cardiomyocyte apoptosis level in rats, and the SalB remedy could alleviate the cardiomyocyte apoptosis caused by CDDP ($p < 0.05$, Fig. 4A–D). At the same time, the apoptosis-related proteins caspase-3, Bax, and Bcl-2 concentrations were also estimated. As expected, it was corroborated in cardiac tissue that SalB remedy declined CDDP-induced caspase-3 and Bax concentrations and increased Bcl-2 concentration ($p < 0.05$, Fig. 4E–H).

The Role of SalB in Reducing Cardiac Toxicity is Related to the Regulation of the Nrf2/ARE Signaling Pathway

To estimate whether SalB can influence CDDP-induced oxidative stress injury through the Nrf2 signaling pathway, the Nrf2/ARE signaling pathway-related proteins were assessed by western blot in this research. It was observed that Nrf2, NQO1, and HO-1 protein levels in rat cardiac tissue induced by CDDP declined, but SalB remedy could increase Nrf2, NQO1, and HO-1 protein levels. This implies that the role of SalB in alleviating cardiotoxicity is related to regulate the Nrf2/ARE signaling pathway ($p < 0.05$, Fig. 5A–D).

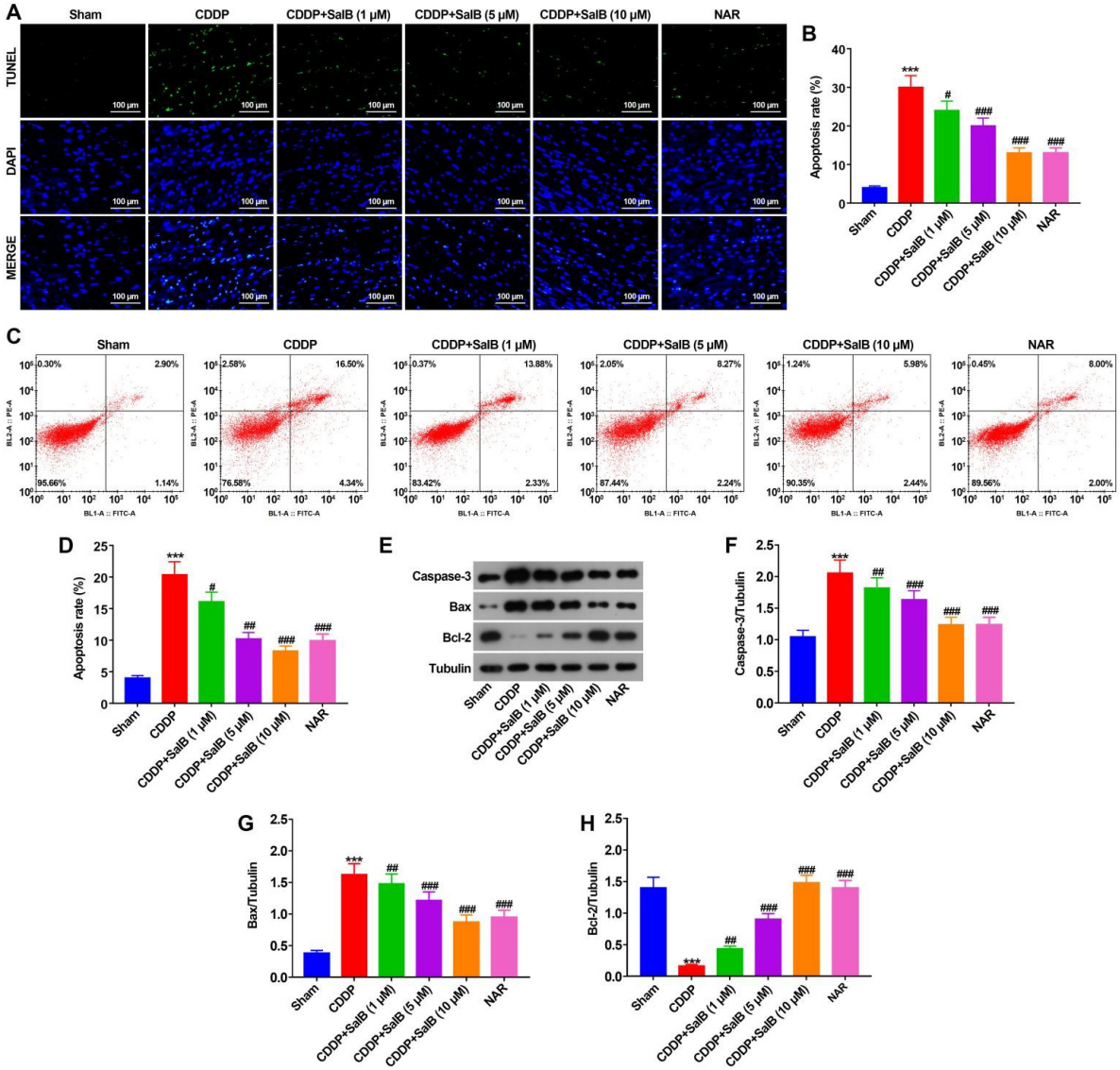

Fig. 4. SalB can lessen CDDP-induced cardiomyocyte apoptosis. (A,B) TdT-mediated dUTP Nick-End Labeling (TUNEL) staining test was utilized for estimating the apoptosis level and apoptosis rate of rat cardiomyocytes (scale bar: 100 μm. Magnification: ×200). (C,D) Flow cytometry was utilized to estimate rat cardiomyocytes' apoptosis level and rate. (E–H) The caspase-3, Bax, and Bcl-2 levels in each subgroup were examined by western blot. Data presented as mean ± SD, $^{***}p < 0.001$, compared to sham subgroup, $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, compared to CDDP subgroup. Bax, Bcl2-Associated X; Bcl-2, B-cell lymphoma-2.

Discussion

CDDP is one of the most utilized chemotherapy drugs in the treatment of solid tumors; however, the toxic effects limit use. The specific mechanism of CDDP-induced cardiotoxicity has yet to be fully elucidated at present. Previous studies have corroborated that CDDP can produce reactive oxygen species and damage the antioxidant defense system, leading to oxidative stress, aggravating damage and heart failure [20].

SalB is a highly active component in the aqueous extract of Salvia miltiorrhiza, which has antioxidant, anti-inflammatory, and anti-fibrosis influences. It has been studied as a potential drug for cardiovascular remedy for many years [21,22]. Li *et al.* [23] have revealed the protective influence of SalB in rats with coronary heart disease through high-throughput and non-targeted lipidomics, indicating that SalB has a good influence on coronary heart disease by regulating glycerophospholipid metabolism, sphingolipid metabolism, and arachidonic acid metabolism, inhibiting oxidative stress injury and lipid peroxidation. In the present research, our results exhibit that SalB has a protective influence on CDDP-induced myocardial injury. In our study, CDDP-induced cardiac dysfunction in rats was characterized by a significant decrease in FS and EF. In addition, CDDP-induced myocardial injury in rats was evident, which was manifested by myocardial fiber disorder and elevated LDH and CK levels in serum. Studies have ex-

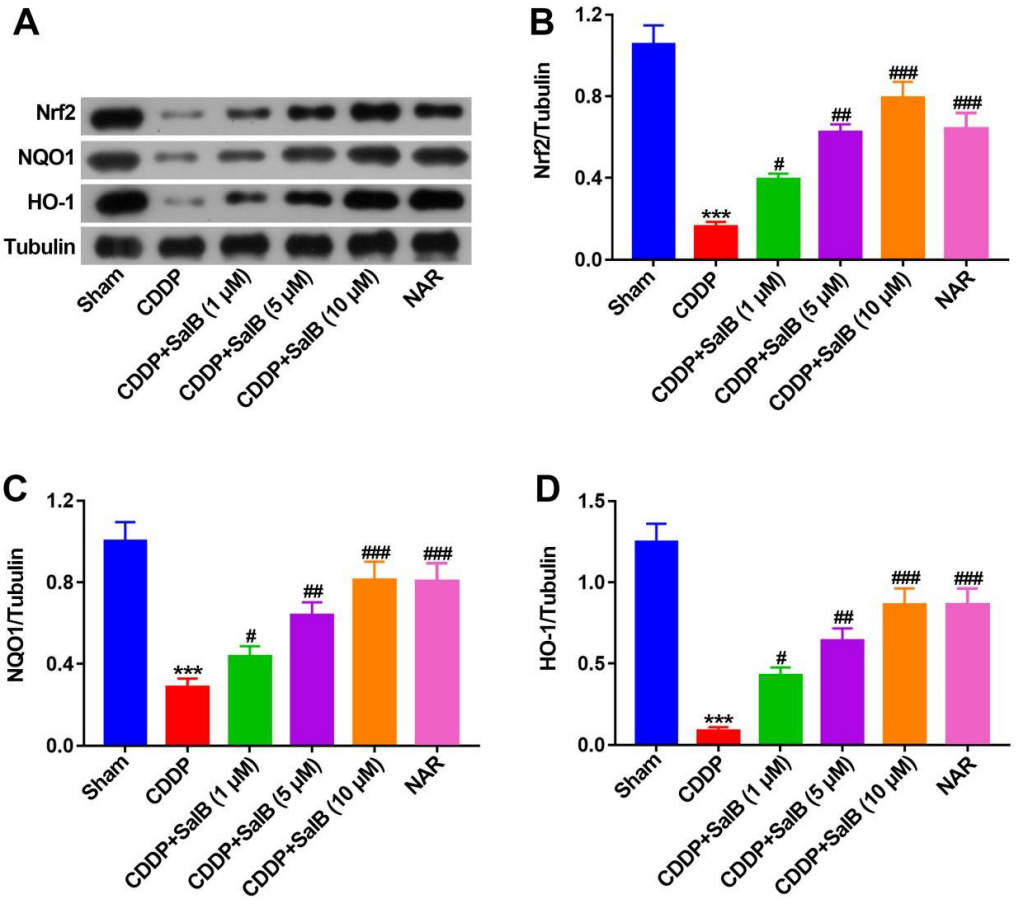

Fig. 5. The role of SalB in alleviating cardiac toxicity is related to the regulation of Nuclear factor E2 related factor 2 (Nrf2). (A) The Nrf2, NAD(P)H quinone oxidoreductase 1 (NQO1), and heme oxygenase-1 (HO-1) levels in each subgroup were examined by western blot. (B–D) Statistical plots of Nrf2, NQO1, and HO-1 protein levels detection. Data presented as mean $\pm$ SD, $^{***}p < 0.001$, compared to sham subgroup; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$, compared to CDDP subgroup.

hibited that CDDP can increase plasma troponin I, CK, and CK-MB levels, which may be the main reason for CDDP-induced cardiac dysfunction [24]. The cardiac function and cardiac injury of rats treated with SalB were alleviated, indicating that SalB has anti-CDDP-induced cardiac toxicity.

In addition, our experimental results showed that the activity and inhibition rate of SOD were declined, and the level of MDA boosted in the myocardial tissue of rats was induced by CDDP; IL-1 β, IL-18, and caspase-1 levels were elevated in serum. TUNEL staining and flow cytometry exhibited that the apoptosis rate of rat cardiomyocytes induced by CDDP was boosted. Research has corroborated that oxidative stress plays a vital role in CDDP-induced cardiotoxicity, and CDDP can lead to mitochondrial dysfunction, nuclear damage, activation of apoptotic pathways, and cardiac tissue inflammation [25]. CDDP induces cardiotoxicity by boosting ROS production. When ROS overproduction exceeds the buffering capacity of the antioxidant defense system, oxidative stress occurs. A large amount of ROS will destroy lipids, proteins and DNA, and lead to cell abnormalities, which will eventually cause heart failure [26]. Research has exhibited that CDDP can boost proinflammatory factors such as IL-1β and TNF-α in myocardial tissue, indicating that CDDP can cause an inflammatory response in cardiac tissue [25]. On the one hand, oxidative stress injury and inflammatory reaction promote each other, and at the same time, they can trigger the influence of apoptosis and cause cardiomyocyte apoptosis [27]. In contrast, rats receiving SalB remedy could enhance CDDP-induced oxidative stress and inflammatory damage and inhibit cardiomyocyte apoptosis.

The Nrf2-ARE pathway plays an endogenous antioxidant role in multiple organs throughout the body. The Nrf2-ARE pathway antagonizes excessive oxidative stress damage in tissues, regulates and activates the Nrf2-ARE pathway to mediate the expression and transcription of a large number of downstream antioxidant enzyme genes such as NQO1 and HO1, thereby exerting antioxidant protective effects [28]. Zhang *et al.* [29] have summarized the natural monomers/extracts that protect against oxidative stress in vascular endothelial cells through the Nrf2/ARE signaling pathway. The results exhibited that the drugs that have a protective influence on oxidative stress of endothelial cells mainly include Phenylpropanes, flavonoids, terpenes, and

biological bases. Most of these drugs (including SalB) can alleviate the apoptosis of endothelial cells caused by oxidative stress; its mechanism is related to the activation of the Nrf2/ARE signaling pathway. This research also estimated the expression of Nrf2/ARE signaling pathway-related proteins. The results exhibited that CDDP could lessen the protein levels of Nrf2, NQO1, and HO-1 in myocardial tissue, while SalB remedy could increase the protein levels of Nrf2, NQO1 and HO-1. This implied that the role of SalB in alleviating cardiac toxicity may be related to the Nrf2 signaling pathway. However, there are shortcomings in this study, which lacked the establishment of an inhibitor and activator group to demonstrate the exact effect on the signaling pathway. In the future, the impact of SalB on cardiotoxicity via the Nrf2/ARE signaling pathway will be further shown by establishing inhibitor and activator groups.

Conclusions

In conclusion, our research revealed the protective influence of SalB on CDDP-induced cardiotoxicity, and its potential function to inhibit oxidative stress, inflammation, and apoptosis through the Nrf2 signaling pathway, thereby improving myocardial injury.

Availability of Data and Materials

The dataset analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

YW and XZ designed the research study. ZL, YB and YL performed the research. YW and XZ analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This experimental protocol has been approved by Sanmen County People's Hospital animal ethics committee (No. 2020-120).

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

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