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Polygonatum polysaccharide attenuates inflammation through inhibiting NLRP3 inflammasome in diabetic cardiomyopathy rats

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RESEARCH PAPER

Abstract

Polygonatum polysaccharide (PP) has good myocardial protection. This study aims to find whether PP can relieve inflammation and play a protective role in diabetic cardiomyopathy (DCM). Intraperitoneal injection of streptozotocin was used to induce DCM in rats, which were then separated into four groups: model group, PP-200 group (200 mg/kg PP), PP-400 group (400 mg/kg PP), and Met group (120 mg/kg metformin). Both control (NC) and model groups of rats were administered normal saline. According to the kit instructions mentioned on the kit, the levels of blood glucose, glycosylated hemoglobin, insulin (INS), and myocardial enzymes (creatinine kinase, B-type natriuretic peptide, and cardiac troponin I) were measured after 8 weeks. Cardiac function was detected by echocardiography. Hematoxylin and eosin (HE) and Masson staining were used to observe pathological changes. Myocardial RNA and protein levels of NLR family pyrin domain containing 3 (NLRP3), caspase-1, and Gasdermin D (GSDMD) were quantified through reverse transcription-polymerase chain reaction and Western blotting analysis. The *in vivo* findings showed that PP could reduce blood glucose, glycosylated hemoglobin, and INS levels, enhance heart functioning, restore histological alterations and myocardial enzymes, and relieve myocardial fibrosis. Furthermore, PP suppressed the expressions of NLRP3, caspase-1, and GSDMD. PP could reduce inflammation in DCM rats by suppressing NLRP3 inflammasome.

Keywords: Polygonatum polysaccharides, NLRP3/Caspase-1 signaling pathway, inflammation, diabetic cardiomyopathy, inflammation, NLRP3–caspase-1 signaling pathway, polygonatum polysaccharides

Introduction

The predominant characteristics of diabetic cardiomyopathy (DCM) include cardiac hypertrophy and fibrosis, excluding coronary heart disease, hypertension, and heart valve disease (Xu *et al.*, 2021). In DCM, progressive cardiac fibrosis results in diastolic dysfunction, which ultimately leads to diminished myocardial contractility and heart failure (Ho *et al.*, 2022). The pathogenesis of DCM is still unclear, but it is considered to be the result of a combination of several factors, such as inflammation, apoptosis, oxidative stress, metabolic disorders, activation of the renin-angiotensin-aldosterone system (RAAS) system, abnormal subcellular components, immune regulation disorders, leading to cardiac interstitial fibrosis, and ventricular remodeling (Kaludercic and Di, 2020;

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Muñoz-Córdova *et al.*, 2021; Tang *et al.*, 2022). Previous research has demonstrated that the nucleotide-binding oligomerization domain-like-receptor family pyrin domain-containing 3 (NLRP3) deficiency enhanced insulin (INS) sensitivity in obese mice, suggesting that NLRP3 plays a crucial role in metabolism (Li *et al.*, 2022). Additionally, another research established that NLRP3 ablation in rats with DCM might greatly decrease myocardial pyroptosis and trigger an inflammatory response (Luo *et al.*, 2017). Myocardial interstitial fibrosis is the pathophysiological basis of DCM, and inflammation plays a significant role in the fibrosis process. NLRP3 inflammasome consists of NLRP3, apoptosis-associated speck-like protein containing a C-terminal caspase-recruitment domain [CARD] (ASC), and caspase-1, which is intimately correlated with myocardial dysfunction in diabetes (Lu *et al.*, 2022b). Therefore, the intervention can prevent and treat DCM by inhibiting the over-activation of NLRP3.

Polygonatum is a widespread genus of *Asparagaceae* family and is extensively distributed in China. It has been used as a medicine or food for over 2000 years, and is utilized in fatty liver disease, Alzheimer's disease, diabetes, cancer, and cardiovascular disease (Liu *et al.*, 2022; Ma *et al.*, 2021; Zhao *et al.*, 2018). Polygonatum includes polysaccharides, steroidal saponins, alkaloids, flavonoids, anthraquinone, and lignans; of these, polygonatum polysaccharide (PP) is the main active component (Wang *et al.*, 2021). PP has various pharmacological activities, including antioxidation, antibacterial, and anti-inflammatory effects, and is used therapeutically to treat diabetes, heart failure, and atherosclerosis (Cui *et al.*, 2018; Wang *et al.*, 2022; Xie *et al.*, 2020). In a previous study, we determined that PP has a protective effect on H9c2 cardiomyocytes injured by hypoxia/reoxygenation (H/R), and its protective mechanism involves blocking the toll-like receptor 4 (TLR4)/MyD88/nuclear factor kappa B (NF-κB) signaling pathway, which downregulates the expression of inflammatory factors in cardiomyocytes, thereby reducing cellular inflammatory response (Lei *et al.*, 2017). Although previous studies have shown that PP can protect H9c2 cardiac cells from H/R damage, it is unclear whether its mechanism prevents and cures DCM by blocking NLRP3 inflammasome activation.

Materials and Methods

Animals

Healthy male Sprague-Dawley (SD) rats were acquired from Pizhou Oriental Breeding Co. Ltd, Pizhou, Jiangsu, China (SCXK (Su) 2017-0003). All experiments complied with the guidelines established by Anhui University of Chinese Medicine's institutional animal care and use committee.

Chemicals and materials

Polygonatum polysaccharide was obtained according to the previous extraction process (Lei *et al.*, 2017). Metformin hydrochloride (6719050) was purchased from Shanghai Xinyi Tianping Pharmaceutical Co. Ltd. Streptozotocin (STZ; Cat. 2196GR001), INS (Cat. RX302147R), B-type natriuretic peptide (BNP; Cat. RX302959R), glycosylated hemoglobin (Cat. RX302312R), and cardiac troponin I (cTNI; Cat. RX301624R) were purchased from Quanzhou Ruixin Biotechnology Co. Ltd. Anti-NLRP3 (ab263899) and anti-Gasdermin D (GSDMD; ab219800) were purchased from Abcam (Cambridge, MA, USA). Anti-glyceraldehyde 3-phosphate dehydrogenase (GAPDH; 380626) was purchased from ZENBIO. Anti-cle-caspase-1 (AF4005) and anti-tubulin (AF7011) were purchased from Affinity Biosciences (Cincinnati, OH, USA). The horseradish peroxidase (HRP)-labeled secondary antibody was purchased from Abbkine (Cat. A21020). Creatinine kinase (CK; A032-1-1) was purchased from Nanjing Jiancheng Institute of Biological Engineering.

Establishment of the rat model

After a week of adaptive feeding, 10 male SD rats were chosen at random for the control (NC) group and fed with a standard diet. Other rats were fed with a high-calorie diet (composition: lard 5%, sugar 5%, yolk powder 5%, and cholesterol 1%). Animal testing was conducted in line with the procedures described by our research group (Shi *et al.*, 2021).

Drug treatment

Successfully modeled SD rats were randomly assigned into the following four groups: model group, PP-200 group (200 mg/kg PP), PP-400 group (400 mg /kg PP), and Met group (120 mg/kg metformin). The same volume of intragastric normal saline was administered to both NC and model groups. All groups received the same intervention for 8 weeks.

Detection of blood glucose-related indicators

After 12 h of fasting, each group of rats was anesthetized with pentobarbital sodium, and blood was collected from the abdominal aorta The supernatant was frozen at −80°C after being centrifuged at 4°C for 15 min at 1500 r/min. Blood glucose, glycosylated hemoglobin, and INS levels were measured following the manufacturer's instructions.

Detection of cardiac function by echocardiography

All rats were sedated with isoflurane, and 2D echocardiography was performed to calculate ejection fraction (EF) and fractional shortening (FS) (Shi *et al.*, 2021).

Detection of pathological staining

Myocardial tissue was fixed at room temperature in 4% paraformaldehyde, dried, embedded in paraffin, and sliced into 5-μm sections. Different sections were stained with hematoxylin and eosin (H&E) and Masson, and viewed under a microscope to evaluate pathological alterations, and collagen volume fraction (CVF).

Detection of myocardial enzymes

The contents of CK, BNP, and cTNI were discovered according to the manufacturer's instructions. CK detection steps were as follows: The serum of rats in each group was collected according to the manufacturer's instructions. After all test solutions were mixed evenly, take a water bath at 45°C for 15 min, the wavelength was adjusted to 660 nm, and the absorbance value of each tube was measured. The enzyme activity of CK was calculated according to the standard curve. BNP and cTNI detection steps were as follows: all Reagents and samples were placed at room temperature, and the working solution in the kit was prepared according to given instructions. Standard wells, zero value wells, blank wells, and sample wells were fixed. Standard substance at different concentrations, 50 μL, was added to each standard well, 50 μL of sample diluent was added to zero value well, and 50 μL of sample to be tested was added to sample well. Horseradish peroxidase (HRP)-labeled detection antibody, 100 μL, was added to standard and sample wells, and incubated at 37°C for 60 min. Each well was filled with washing liquid for 20 s; washing liquid was removed, and the process was repeated for five times. Matrix mixture, 100 μL, was added to all wells. Reaction plate was covered with a sealing film and incubated at 37°C for 15 min. Finally, 50 μL of stop solution was added to all wells, and absorbance (OD value) was read on a microplate reader.

Detection of mRNA expression using RT-PCR

mRNA in myocardial tissue was extracted from the left ventricular myocardium using trizol reagent. Reverse transcription-polymerase chain reaction (RT-PCR) was conducted with the LightCycler® 96 PCR apparatus (Roche, Switzerland). The results were analyzed using $2^{-\Delta\Delta Cq}$ method to evaluate the mRNA levels of NLRP3, caspase-1, and GSDMD. The primers used in the research are shown in Table 1.

Table 1. Primers used in RT-qPCR.

Primers	Sequence (5' → 3')	
NLRP3	Forward	5'-GAGCTGGACCTCAGTGACAATGC-3'
	Reverse	5'-AGAACCAATGCGAGATCCTGACAAC-3'
Caspase-1	Forward	5'-GCACAAGACTTCTGACAGTACCTTCC-3'
	Reverse	5'-GCTTGGGCACTTCAATGTGTTCATC-3'
GSDMD	Forward	5'-CAGCAGGCAGCATCCTTGAGTG-3'
	Reverse	5'-CCTCCAGAGCCTTAGTAGCCAGTAG-3'
β-actin	Forward	5'-CCCATCTATGAGGGTTACGC-3'
	Reverse	5'-TTTAATGTCACGCACGATTTC-3'

Detection of protein expression by Western blotting analysis

Heart tissue (0.1 g) was lysed in lysate, and total proteins were extracted. The antibody concentrations were as follows: anti-NLRP3 (1:1000), anti-cleaved caspase-1 (1:1000), anti-GSDMD (1:1000), anti-GAPDH (1:5000), and anti-tubulin (1:5000). The primary antibody was incubated overnight at 4°C before being incubated at room temperature with the secondary antibody for 2 h. The density of protein bands was detected using ECL chemical substrate luminescence kit, and the protein bands were imaged in Tanon5200 imaging system (Tanon, China).

Statistical analysis

The data were given as mean ± standard deviation (SD), and statistical analysis was performed using SPSS 23.0. One-way ANOVA was used to determine significance between groups, and $p < 0.05$ was considered statistically significant.

Results

PP reduced blood glucose levels in model rats

Abnormal blood glucose levels suggested that the DCM model was developed properly. After 8 weeks, the model group had considerably higher blood glucose and glycosylated hemoglobin levels than the NC group ($p < 0.01$); the model group also had significantly lower INS level than the NC group ($p < 0.01$). The levels of blood glucose, glycosylated hemoglobin, and INS were reversed following treatment with metformin and PP ($p < 0.05$ and

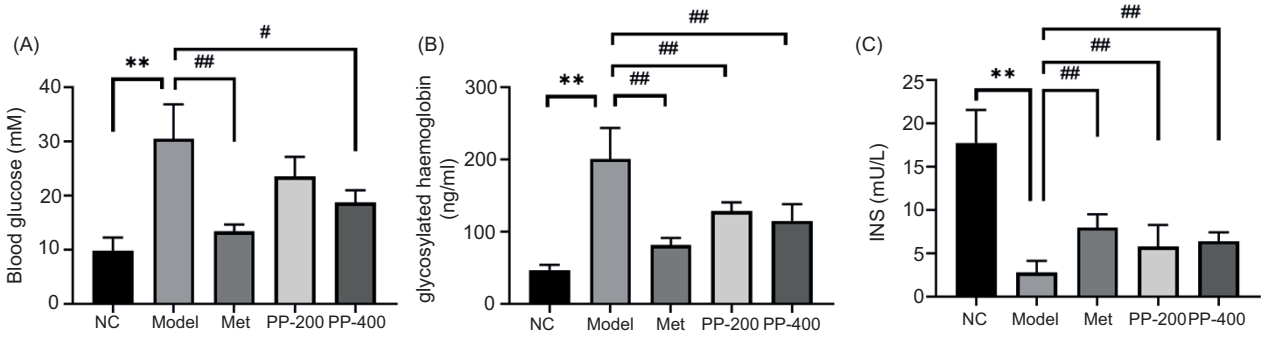

Figure 1. Polygonatum polysaccharide reduced blood glucose levels in model rats. (A) Blood glucose; (B) glycosylated hemoglobin; and (C) insulin. The values were expressed as mean ± SD (n = 10), $^{**}p < 0.01$ vs. control group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. model group.

<0.01, respectively; Figure 1). PP could effectively reduce blood glucose levels in model rats.

PP improved heart function in model rats

Echocardiography was performed to determine the heart function of rat in each group of rats, with EF and FS serving as primary indices. EF and FS values of the model group were considerably lower than those of the NC group ($p < 0.01$); however, FS and left ventricular ejection fraction (LVEF) values were reversed in both PP-400 and Met groups ($p < 0.05$ and < 0.01, respectively; Figure 2). The results suggested that PP had a certain ameliorative effect on diabetic cardiac function injury.

PP improved histopathological changes in model rats

The NC group exhibited normal morphology, complete myocardial structure, and an ordered arrangement of muscle fibers, as shown by H&E staining. The model group exhibited myocardial fracture, myocardial fiber organization abnormality, and inflammatory cell infiltration. Myocardial fibers of both Met and PP groups were arranged in a relatively orderly manner with a small amount of inflammatory infiltration (Figure 3). The findings indicated that PP could greatly mitigate the progression of heart disease.

PP alleviated myocardial fibrosis in model rats

Masson staining revealed that muscle fibers of the myocardium were red and collagen fibers were blue. In the NC group, myocardial fibers were organized and only a small amount of collagen fibers was formed whereas the model group had abundant collagen fiber depositions. Pretreatment with PP and metformin, resulted in a significant reduction of collagen content of heart tissue. CVF level was considerably higher in the model group than in the NC group ($p < 0.01$), and PP and metformin were able to reduce the amount of CVF ($p < 0.01$; Figure 4).

PP improved myocardial enzymes in model rats

Levels of CK, BNP, and cTNI were considerably higher in the model group than in the NC group ($p < 0.01$), but PP and metformin significantly lowered these levels ($p < 0.01$) (Figure 5). The results showed that PP could significantly reduce myocardial enzymes in model rats.

PP inhibited mRNA and protein expressions of NLRP3, caspase-1, and GSDMD

Compared to the NC group, mRNA and protein levels of NLRP3, caspase-1, and GSDMD increased considerably in the model group ($p < 0.05$ and < 0.01, respectively). On the other hand, mRNA and protein expressions of NLRP3, caspase-1, and GSDMD were reversed ($p < 0.05$ and < 0.01, respectively) following treatment with PP and metformin (Figure 6). These results suggested that PP played a protective role in the myocardium by acting on the NLRP3/caspase-1/GSDMD signaling pathway.

Discussion

The pathological characteristics of DCM include myocardial interstitial fibrosis, cardiomyocyte apoptosis, and cardiomyocyte hypertrophy, which eventually leads to myocardial remodeling. The clinical feature is diastolic dysfunction, and systolic dysfunction can also occur in the late stage (Salvatore *et al.*, 2021). At present, there is no effective treatment for DCM. The basic principle of treatment is to actively control blood glucose and combine cardiovascular protective drugs according to individual differences, such as statins, angiotensin-converting

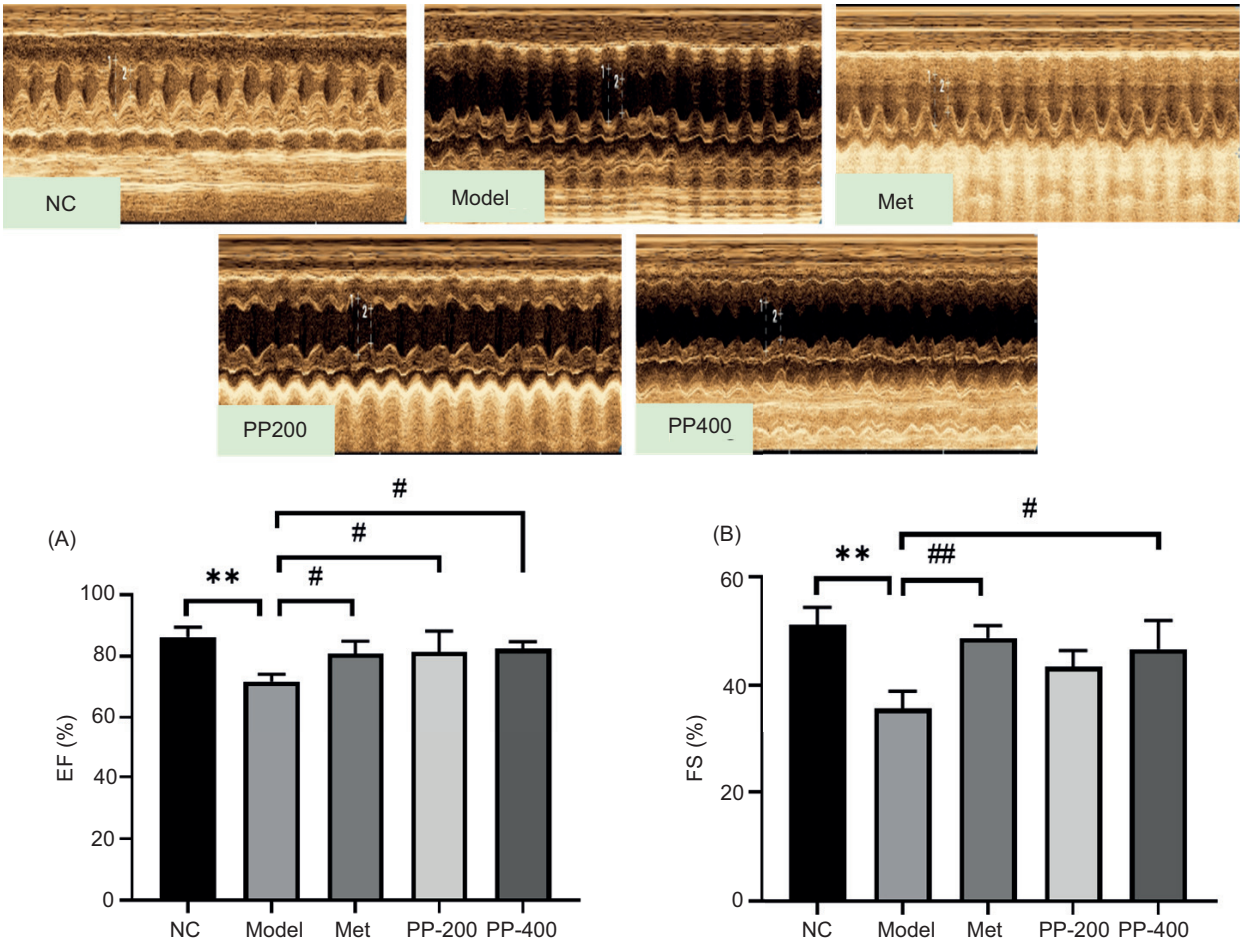

Figure 2. Polygonatum polysaccharide improved heart functioning in model rats. (A) Ejection fraction (%); and (B) fractional shortening (%). The values were expressed as mean ± SD (n = 10), $^{**}p < 0.01$ vs. control group; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. model group.

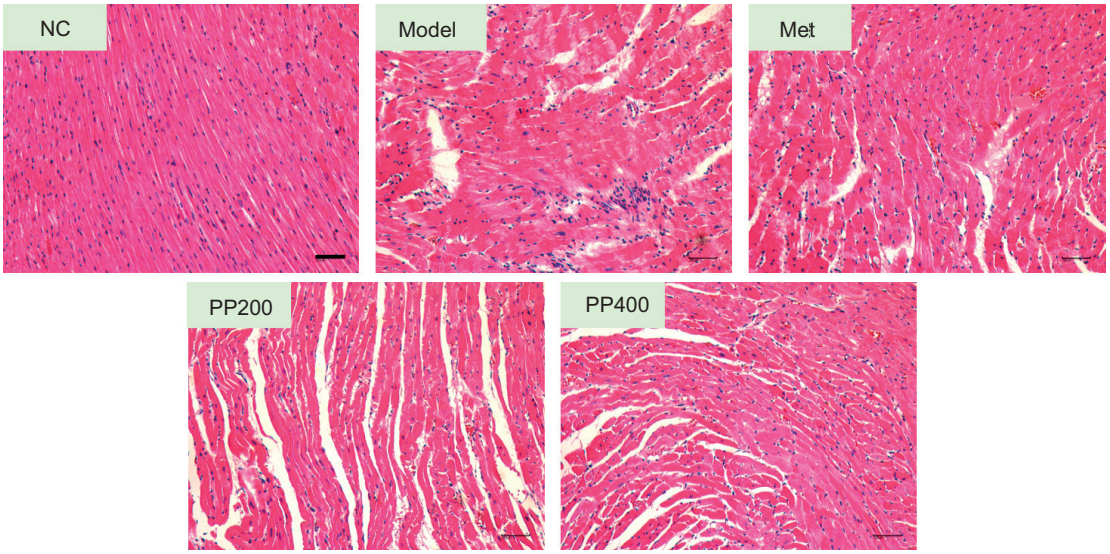

Figure 3. Polygonatum polysaccharide improved histopathological changes in model rats.

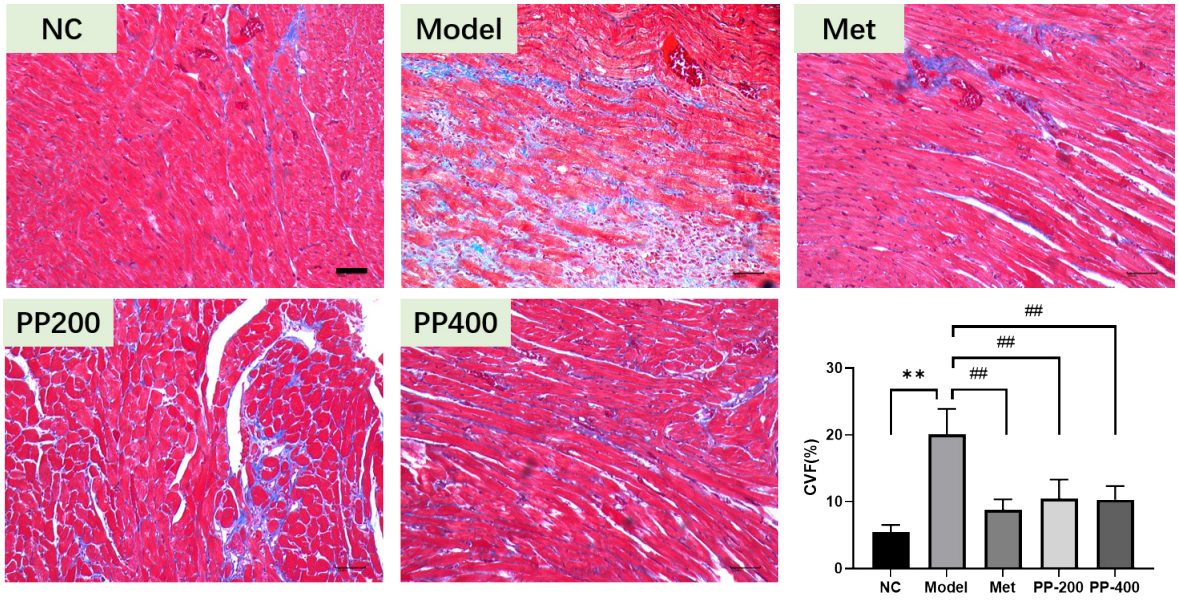

Figure 4. Polygonatum polysaccharide alleviated myocardial fibrosis in model rats.

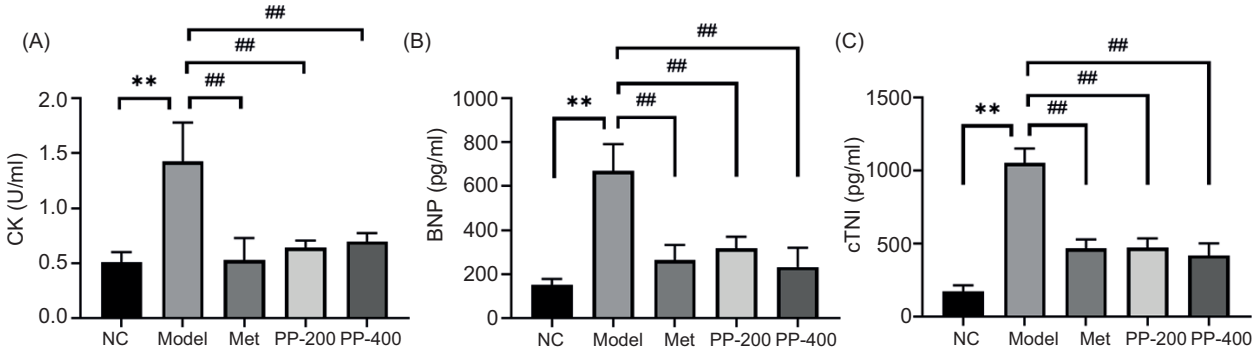

Figure 5. Polygonatum polysaccharide improved myocardial enzymes in model rats. (A) Creatinine kinase (U/mL); (B) B-type natriuretic peptide (pg/mL); and (C) cardiac troponin I (pg/mL). The values were expressed as the mean ± SD (n = 10), **$p < 0.01$ vs. control group; ##$p < 0.01$ vs. model group.

enzyme inhibitor–angiotensin receptor blocker (ACEi/ARB), and β-receptor blockers, which can achieve therapeutic effects (Wang and Tang, 2011). Therefore, drug research on target genes, key molecular receptors, cytokines, and mechanisms of DCM has gradually become a research hotspot. After being stimulated by hyperglycemia, the body over-activates NLRP3 inflammasome. The specific process is that NLRP3 oligomerizes and interacts with ASC to recruit pro-caspase-1, then activate caspase-1, and cut GSDMD to release GSDMD-N domain that can form pores on cell membranes. The pores on cell membranes release inflammatory substances, produce inflammatory cascade reaction, promote myocardial remodeling, and elevate the course of DCM (Lu *et al.*, 2022a; Wu *et al.*, 2021). Therefore, inhibiting the activation of NLRP3 inflammasome and alleviating inflammatory response can significantly improve the myocardial remodeling of diabetes.

In recent years, plant polysaccharides as a class of natural products have been the subject of intensive investigation. Numerous studies have demonstrated that plant polysaccharides could improve cardiovascular diseases by anti-oxidative stress, restoring the metabolism of biological macromolecules, regulating apoptosis, and inhibiting inflammatory signal pathways (Dong *et al.*, 2021; Zhou *et al.*, 2021). In particular, polysaccharides have a good role in the prevention and treatment of DCM. Lycium barbarum polysaccharide decreases expressions of atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and calpain-1. It also decreases the protein expression of interlukin (IL)-6, tumor necrosis

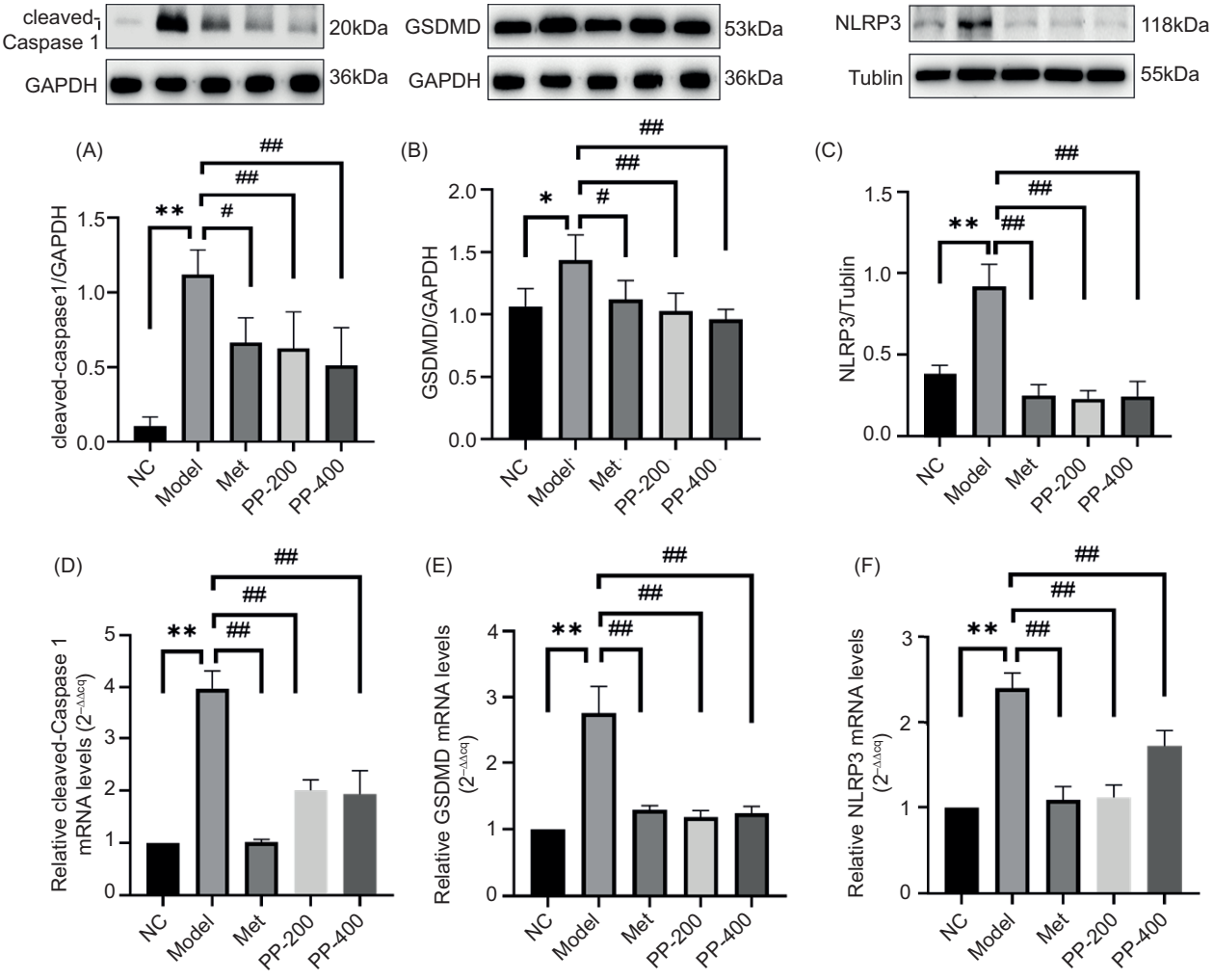

Figure 6. Polygonatum polysaccharide inhibited mRNA and protein expressions of NLRP3, caspase-1, and GSDMD. (A) Cle-aspase-1 protein; (B) GSDMD protein; (C) NLRP3 protein; (D) caspase-1 mRNA; (E) GSDMD mRNA; and (F) NLRP3 mRNA. The values were expressed as mean ± SD (n = 3), *$p < 0.05$, **$p < 0.01$ vs. control group; #$p < 0.05$, ##$p < 0.01$ vs. model group.

factor-α (TNF-α), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and toll-like receptor 4 (TLR4) in diabetic heart tissue, and alleviated ventricular hypertrophy in diabetic rats through suppressing the activation of NF-κB (Liu *et al.*, 2019). In rats with DCM, astragalus polysaccharide could enhance cardiac functioning and minimize cardiomyocyte apoptosis, which involved the down-regulation of cardiomyocyte apoptosis by reducing the expression of activating transcription factor 6 (ATF6) and protein endoplasmic reticulum kinase (PERK)-associated endoplasmic reticulum (ER) stress pathway proteins (Sun *et al.*, 2019). Through the sterol regulatory element-binding protein-1–stearoyl-CoA desaturase-1 (SREBP-1/SCD-1) axis, *Arctium lappa* L. (greater burdock) polysaccharide may effectively control lipid metabolism and minimize the risk of atherosclerosis in type 2 diabetic rats (Chen *et al.*, 2020). Therefore, polysaccharides can prevent and treat DCM mainly through anti-inflammatory, anti-apoptotic, and regulating lipid metabolism mechanisms.

At present, the cardiovascular protective effect of PP has been reported in the literature. PP could regulate oxidative stress and inflammation in rats with autoimmune myocarditis and diminish pathological damage and fibrosis in cardiac tissues through activating the Janus kinase–signal transducer and activator of transcription protein (JAK/STAT3) signaling pathway (Yin *et al.*, 2021). PP could protect against isoproterenol-induced cardiac remodeling damage and diminish the expression of ICAM-1 and VCAM-1 in myocardial tissue because of its antioxidant and anti-inflammatory properties (Ma *et al.*, 2018). PP might enhance heart rate and left ventricular systolic pressure. It could reduce serum cTnI, creatine kinase myocardial band (CK-MB), TNF-α, IL-6,

malondialdehyde (MDA), myocardial Bax, and cleaved caspase-3 protein expression levels, thereby preventing adriamycin-induced acute heart failure (Zhu *et al.*, 2018). PP reduces myocardial damage in acute myocardial infarction (AMI)-model rats, which can be due to an increase in superoxide dismutase (SOD) level in myocardial tissue, a decrease in MDA and ROS levels, and regulation of the Wnt–β-catenin pathway (An *et al*., 2021). However, there are only few studies on the protective effect of PP on DCM, and the purpose of this study was to determine whether PP could prevent DCM by suppressing the NLRP3 signal pathway.

In this study, *in vivo* experiments demonstrated that PP could protect injured myocardium in DCM by decreasing blood glucose levels, enhancing cardiac function, decreasing histological alterations and myocardial enzymes, and relieving myocardial fibrosis. PP could also suppress the mRNA and protein expressions of NLRP3, caspase-1, and GSDMD in DCM. The results indicated that PP could be used to prevent and cure DCM, and the protective effect was associated with its regulatory NLRP3caspase-1 signaling pathway.

Conclusion

We confirmed that PP could significantly prevent the occurrence and development of DCM from the aspects of cardiac function, myocardial enzymes, histopathology, and signal pathway. The mechanism was related to the NLRP3/caspase-1 signaling pathway. In this study, *in vivo* animal experiments partially revealed the mechanism of PP in reducing DCM injury. Further research is required to focus on gene silencing to act on cardiomyocytes *in vitro*, and clarify the mechanism of PP in preventing and treating DCM.

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Author Contributions

ANL and HS designed the study and revised the manuscript. CCZ, MZ, JFP, and YYM carried out the experiments. XNZ, ZYW and SSW analyzed the data. The manuscript was written and revised by CCZ and MZ. All authors approved the final version of the paper.

Conflict of Interest

The authors declared that they had no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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