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ORIGINAL RESEARCH

Astragaloside IV improves myocardial injury in rats with insulin-resistant heart failure

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Abstract

Heart failure is a common cardiovascular condition, with insulin resistance emerging as the predominant risk factor associated with its development. Astragaloside IV (AS-IV) is one of the important active components of *Astragalus membranaceus* (Fisch.) Bunge, and this drug has been reported to participate in heart failure progression. Nevertheless, the regulatory effects and related mechanisms of AS-IV in heart failure with insulin resistance have not been fully elucidated. *In vitro* experiments, groups were separated into the Con, almitic acid (PA), PA + AS-IV 0.25 μM, PA + AS-IV 0.5 μM, PA + AS-IV 1 μM and PA + Metoprolol groups. *In vivo* experiments, groups were separated into the Control, Abdominal aorta coarctation (AAC), AAC + AS-IV (20 mg/kg), AAC + AS-IV (40 mg/kg), AAC + AS-IV (80 mg/kg) and AAC + Metoprolol groups. In this study, it was illustrated that AS-IV improved cell viability in H9c2 cells triggered by PA. Furthermore, AS-IV improved the heart function in rats with heart failure caused by insulin resistance. AS-IV demonstrated the ability to reduce damage to the heart muscle. Subsequently, it was observed that AS-IV eased insulin resistance and reduced inflammation. Finally, research confirmed that AS-IV inhibited the p38 pathway and activated the protein kinase B (Akt) pathway both *in vivo* and *in vitro* settings. In summary, the findings of this study indicate that AS-IV has the potential to enhance heart function in cases of insulin-resistant heart failure, both in experimental and laboratory conditions.

Keywords

Astragaloside IV; Myocardial injury; Insulin-resistant heart failure; The p38 pathway

1. Introduction

Heart failure is a common cardiac condition that, in severe instances, can result in fatalities [1, 2]. Recently, the prevalence of this disease continues to escalate [2]. Heart failure is a multifaceted condition that can be induced by a variety of factors, including but not limited to diabetes, hypertension, obesity or coronary heart disease [3]. Insulin resistance plays a key role in left ventricular dysfunction and is the primary risk factor for heart failure [4]. Insulin resistance may also result into cardiac remodeling and ventricular dysfunction through the modulation of insulin concentration and sensitivity [5]. Hence, it is crucial to have a thorough understanding of the intricate mechanisms underlying insulin-resistant heart failure and to explore innovative therapeutic medications.

Astragalus membranaceus (Fisch.) Bunge (Chinese name: Huangqi) and other traditional Chinese herbs have a long history for heart failure treatment, and they have many advantages such as low cost and few side effects [6]. Astragaloside IV (AS-IV) is one key active component of *Astragalus membranaceus* (Fisch.) Bunge. AS-IV has many pharmacological effects (such as anti-virus, anti-inflammation and anti-oxidation) [7], and exists vital regulatory functions in heart failure. For instance, AS-IV has the capability to regulate the activity of small ubiquitin-like modifier (SUMO)-specific protease 1, thus enhancing heart failure [8]. In addition, AS-IV affects nuclear factor erythroid 2-related factor 2 (Nrf-2) to relieve heart failure [9]. Moreover, AS-IV has been shown to mitigate ventricular remodeling and regulate fatty acid levels in rats suffering from chronic heart failure [10]. Besides, AS-IV can generate fatty acid β-oxidation from switching glycolysis, thereby ameliorating heart failure [11]. Remarkably, AS-IV has the ability to reinstate the nitric oxide (NO) signaling, thereby improving left ventricular diastolic dysfunction and lowering insulin levels [12]. However, the regulatory impacts and associated pathways of AS-IV in insulin-resistant heart failure keep vague.

In this study, it is aimed to explore the regulatory functions of AS-IV and associated pathway in insulin-resistant heart failure. This work may provide novel opinions and illustrate a valid drug-AS-IV for ameliorating heart failure.

2. Materials and methods

2.1 Cell culture and treatment

Rat H9c2 cells were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). Cells were cultured with Dulbecco's modified eagle medium (DMEM) including 10% fetal bovine serum in one incubator with 5% CO_2 at 37 °C for 24 h.

Palmitic acid (PA, 400 μM, Sigma-Aldrich; Merck KGaA, Darmstadt, HE, Germany) was employed to treat H9c2 cells for 24 h to establish myocardial injury *in vitro* model.

AS-IV (0.25, 0.5 and 1 μM; purity >98%; Shanghai Ronghe Co., Shanghai, China) was utilized to treat H9c2 cells for 24 h.

Metoprolol (2×10^{-5} mol/L, ab120711, Abcam, Shanghai, China) was utilized to treat H9c2 cells for 24 h.

2.2 Cell counting kit-8 (CCK-8) assay

In the 96-well plate, H9c2 cells were placed (1000 cells/well). CCK-8 solution (10 μL, Dojindo Laboratories, Kumamoto, Japan) was mixed into each well for 4 h incubation. Eventually, cell viability was verified through the spectrophotometer (ND-ONE-W, Thermo Fisher Scientific, Waltham, MA, USA).

2.3 Rat model

The male Wistar rats (total n = 36, n = 6/group) were obtained from Shanghai Slac Laboratory Animal Co. Ltd (Shanghai, China). Rats were provided with unlimited access to water and food, and maintained on a 12-hour light/dark cycle. The animal studies were conducted in accordance with the guidelines set forth in the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and this work was gained the approval from the Animal Care and Use Committee of the First Affiliated Hospital of Guizhou University of Traditional Chinese Medicine.

There are six groups (n = 6 rats in each group):

(1) Control group;

(2) AAC group;

(3) AAC + AS-IV (20 mg/kg) group;

(4) AAC + AS-IV (40 mg/kg) group;

(5) AAC + AS-IV (80 mg/kg) group;

(6) AAC + Metoprolol group.

After anesthesia (3% pentobarbital sodium, intraperitoneal injection), laparotomy was done. Abdominal aorta coarctation (AAC) in rats was made to mimic heart failure with insulin resistance [13, 14]. The abdominal artery was exposed and ligated using a 6/0 silk suture, resulting in a constriction of 65%–70%. Rats in the AAC + AS-IV group received AS-IV treatment (20, 40 and 80 mg/kg) for 14 days via oral gavage [15]. In the Control group, rats were undergone the same procedure except the ligation. In the AAC + Metoprolol group, AAC rats were treated with Metoprolol (10 mg/kg) for 14 days by gavage.

2.4 Hemodynamic monitoring

After anesthesia, the left ventricular (LV) chamber was inserted with the conductance micromanometer catheter (1.4F, Millar Instruments, Houston, TX, USA) through the left carotid artery. The LV systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), maximum of the first differentiation of LV pressure (LV + dp/dt_{max}) and decline (LV − dp/dt_{max}) were obtained under the PowerLab data acquisition system (AD Instruments, Sydney, NSW, Australia).

2.5 Hematoxylin & eosin (HE) staining

The myocardial tissues were fixed with 4% paraformaldehyde for 24 h. Next, paraffin-embedding was performed, and then samples were cut into 4-μm thick sections. Following the dewaxing process and rehydration with xylene and gradient alcohol, the staining procedure was carried out for the sections using hematoxylin for 5 minutes and eosin for 30 seconds. Subsequently, the sections were dehydrated with alcohol and then sealed using a neutral mounting medium. Lastly, the pathological changes of myocardial tissues were observed through the light microscope (CX41, Olympus Corporation, Tokyo, Japan).

2.6 Detection of FBG, fasting insulin (FIN), HOMA-IR, FFA

Blood samples were obtained from the rats' tails to assess their fasting blood glucose (FBG) levels. The FBG levels were analyzed using the FreeStyle Lite blood glucose meter (4073343, Abbot Diabetes Care, Inc., Alameda, CA, USA).

Rat blood samples were obtained from the abdominal aorta and transferred into a sterile test tube containing the necessary anticoagulant. Following centrifugation, the resulting supernatant (serum) was meticulously extracted. The quantification of serum insulin was conducted using an enzyme immunoassay on an AIA 1200 analyzer (Tosoh, Tokyo, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated: HOMA-IR = (FBG (mmol/L) $\times$ FIN (μIU/mL)/22.5. The serum free fatty acid (FFA) was inspected using the commercial kit (A042-1-1, Jian Cheng Biological Engineering Institute, Nanjing, Jiangsu, China).

2.7 Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

RNAs were separated from myocardial tissues through using the Trizol reagent (15596018, Thermo Fisher Scientifc, Waltham, MA, USA). The synthesis of cDNA from RNA molecules was carried out using the PrimeScript™ RT Reagent Kit (RR037A, Takara, Dalian, Liaoning, China). Next, RT-qPCR was made through the SYBR Green PCR kit (QPK-201, Toyobo, Osaka, Japan). The mRNA expressions were obtained using the $2^{-\Delta\Delta Ct}$ method.

The primers were listed:

Tumor Necrosis Factor-α (TNF-α):

F: 5′ GAGGCCAAGCCCTGGTATG 3′,

R: 5′ CGGGCCGATTGATCTCAGC 3′;

Interleukin 6 (IL-6):

F: 5′ ACTCACCTCTTCAGAACGAATTG 3′,

R: 5′ CCATCTTTGGAAGGTTCAGGTTG 3′;

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH):

F: 5′ GCCACAACGACCCCTTCATG 3′,

R: 5′ TGCCAGTGAGCTTCCCGTTC 3′.

2.8 Western blot

The extraction of proteins from myocardial tissues was made using the radio immunoprecipitation assay (RIPA) lysis buffer. Proteins were separated using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) followed by transfer onto a polyvinylidene difluoride membrane (PVDF, Sigma, St Louis, USA). The membranes were incubated with primary antibodies for 12 hours, followed by incubation with a secondary antibody (1/1000; ab6721, Abcam, Shanghai, China) for 2 hours. Protein bands were detected using the enhanced chemiluminescence kit (20148, Thermo Fisher Scientific, Waltham, MA, USA) for analysis.

The primary antibodies: p-p38 (1/1000; ab178867), p38 (1/1000; ab45136), p-Akt (1/500; ab38449), Akt (1/2000; ab8805) and β-actin (1 μg/mL; ab8226).

2.9 Statistical analysis

SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) were utilized for statistical analysis. Data were exhibited as mean $\pm$ standard deviation (SD). The research employed one-way Analysis of Variance (ANOVA) with Tukey's *post hoc* test to compare multiple groups. $p < 0.05$ was regarded as statistical significance.

3. Results

3.1 Astragaloside IV improved cell viability in H9c2 cells triggered by PA

Cell viability was altered following treatment with different concentrations of AS-IV (0.25, 0.5 and 1 μM), showing a decrease in viability after exposure to higher concentrations of AS-IV (2 and 4 μM) ($p < 0.001$) (Fig. 1A). Furthermore, cell viability was attenuated after PA induction, but this change was offset after AS-IV treatment (0.5 and 1 μM) or Metoprolol treatment (positive control) ($p < 0.001$) (Fig. 1B). Moreover, the lactate dehydrogenase (LDH) concentration increased significantly following PA stimulation ($p < 0.001$). However, this effect was ameliorated by treatment with AS-IV (0.25, 0.5 and 1 μM) or Metoprolol ($p < 0.01$) (Fig. 1C). In general, Astragaloside IV improved cell viability in H9c2 cells triggered by PA.

3.2 Astragaloside IV affected cardiac hemodynamics in rat model with insulin-resistant heart failure

In AAC rats, the LVSP showed a significant decrease ($p < 0.001$); however, this effect was reversed following treatment with AS-IV (at doses of 40 and 80 mg/kg) or Metoprolol ($p < 0.001$) (Fig. 2A). The reversed changes had occurred in LVEDP ($p < 0.001$) (Fig. 2B). The LV + dp/dt$_{max}$ and LV − dp/dt$_{max}$ were both reduced in AAC rats ($p < 0.001$), but these impacts were counteracted after AS-IV treatment (40 and 80 mg/kg) or Metoprolol treatment ($p < 0.05$) (Fig. 2C,D). Collectively, Astragaloside IV influenced the cardiovascular function in a rat model of heart failure with insulin resistance.

3.3 Astragaloside IV alleviated myocardial injury

In the AAC rats, an increase in the size of myocardial cells, presence of necrotic myocardial cells, and significant inflammatory infiltration were observed. However, these effects were reversed upon administration of AS-IV (at doses of 40 and 80 mg/kg) or Metoprolol treatment (Fig. 3), indicating that Astragaloside IV alleviated myocardial injury.

3.4 Astragaloside IV affected insulin-resistant and alleviated inflammation

The FBG and FIN levels were increased in AAC rats ($p < 0.001$), but these changes were neutralized after AS-IV treatment (40 and 80 mg/kg) or Metoprolol treatment ($p < 0.05$) (Fig. 4A,B). Subsequently, there was a noticeable increase in HOMA-IR levels observed in the AAC rats ($p < 0.001$). However, following the administration of AS-IV at doses of 40 and 80 mg/kg, or Metoprolol treatment, this effect was mitigated significantly ($p < 0.001$) (Fig. 4C). The serum FFA was aggrandized in AAC rats ($p < 0.001$), but this phenomenon was attenuated after AS-IV treatment (40 and 80 mg/kg) or Metoprolol treatment ($p < 0.05$) (Fig. 4D). In AAC rats, the levels of TNF-α and IL-6 mRNA in the serum showed a significant increase ($p < 0.001$). However, this elevation was effectively reversed following the administration of AS-IV (at doses of 40 and 80 mg/kg) or Metoprolol ($p < 0.001$) (Fig. 4E,F). Collectively, Astragaloside IV had an impact on insulin resistance and mitigated inflammation.

3.5 Astragaloside IV retarded the p38 pathway

In vivo, the p-p38/p38 level was up-regulated as well as p-Akt/Akt level was down-regulated in AAC rats ($p < 0.001$), but these changes were rescued after AS-IV treatment (40 and 80 mg/kg) or Metoprolol treatment ($p < 0.001$). Similarly, in the *in vitro* setting, comparable alterations were observed in the levels of p-p38/p38 and p-Akt/Akt in H9c2 cells stimulated by PA ($p < 0.05$) (Fig. 5). Simply put, Astragaloside IV has the ability to slow down the p38 pathway and promote the Akt pathway both in living organisms and in laboratory studies.

4. Discussion

Many extracts from Chinese herbs own improvement effects on the progression of heart failure [16]. AS-IV has also been verified to ameliorate heart failure [8–10]. Nonetheless, the regulatory effects and underlying mechanisms of AS-IV in heart failure induced by insulin resistance are still poorly understood. This research demonstrated that AS-IV enhanced the viability of H9c2 cells exposed to PA. Moreover, AS-IV affected cardiac hemodynamics in rat model with insulin-resistant heart failure. AS-IV can alleviate myocardial injury.

Insulin resistance is the cause and outcome of heart failure, and leads to worse prognosis in patients with heart failure [17]. In cases of insulin resistance, an increase in the plasma concentration of free fatty acids is a common metabolic abnormality

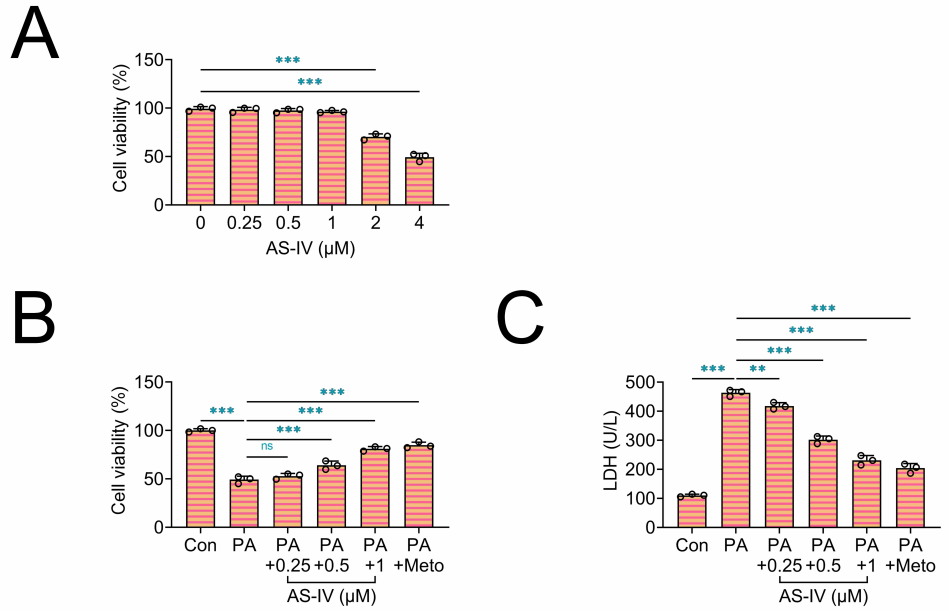

FIGURE 1. Astragaloside IV modulated cell viability in H9c2 cells triggered by PA. (A) In the 0, 0.25, 0.5, 1, 2 and 4 μM AS-IV groups, cell viability of H9c2 cells was confirmed through CCK-8 assay. (B) In the Con, PA, PA + AS-IV 0.25 μM, PA + AS-IV 0.5 μM, PA + AS-IV 1 μM and PA + Metoprolol groups, cell viability was examined through CCK-8 assay. (C) In the Con, PA, PA + AS-IV 0.25 μM, PA + AS-IV 0.5 μM, PA + AS-IV 1 μM and PA + Metoprolol groups, LDH level was evaluated through the LDH kit. $^{**}p < 0.01$, $^{***}p < 0.001$. AS-IV: Astragaloside IV; PA: almitic acid; Con: Control; LDH: lactate dehydrogenase; ns: no significance.

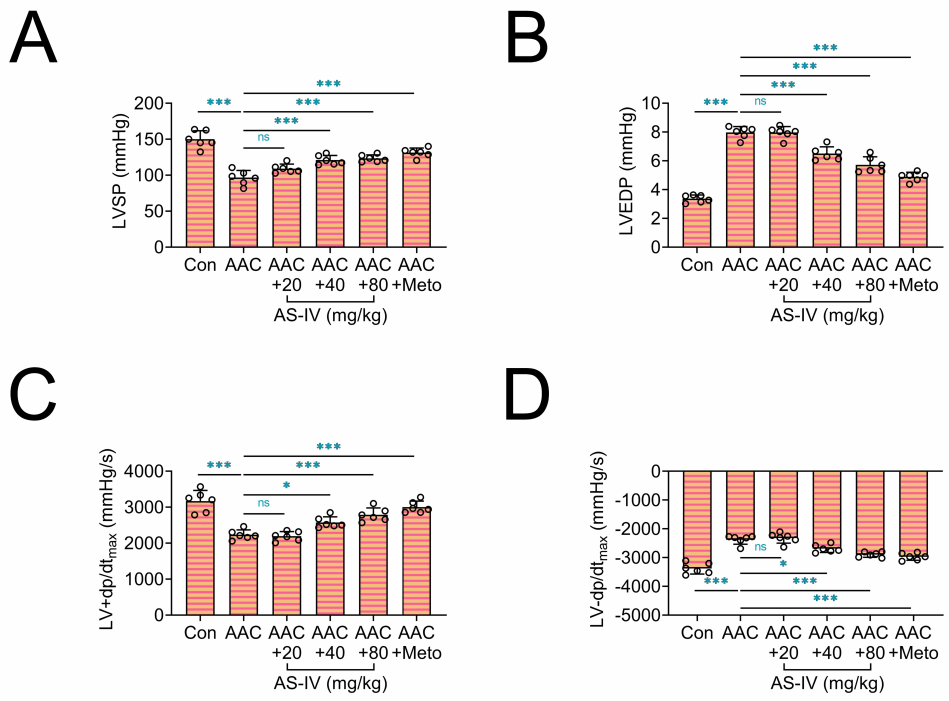

FIGURE 2. Astragaloside IV affected cardiac hemodynamics in rat model with insulin-resistant heart failure. Groups were separated into the Control, AAC, AAC + AS-IV (20 mg/kg), AAC + AS-IV (40 mg/kg), AAC + AS-IV (80 mg/kg) and AAC + Metoprolol groups. (A,B) The left ventricular systolic pressure (LVSP) and left ventricular end-diastolic pressure (LVEDP) were verified through hemodynamic monitoring. (C,D) The maximum of the first differentiation of LV pressure (LV + dp/dt$_{max}$) and decline (LV − dp/dt$_{max}$) were assessed through hemodynamic monitoring. $^{*}p < 0.05$, $^{***}p < 0.001$. AS-IV: Astragaloside IV; LVSP: LV systolic pressure; Con: Control; AAC: Abdominal aorta coarctation; Meto: Metoprolol; LVEDP: LV end-diastolic pressure; LV: left ventricular; ns: no significance.

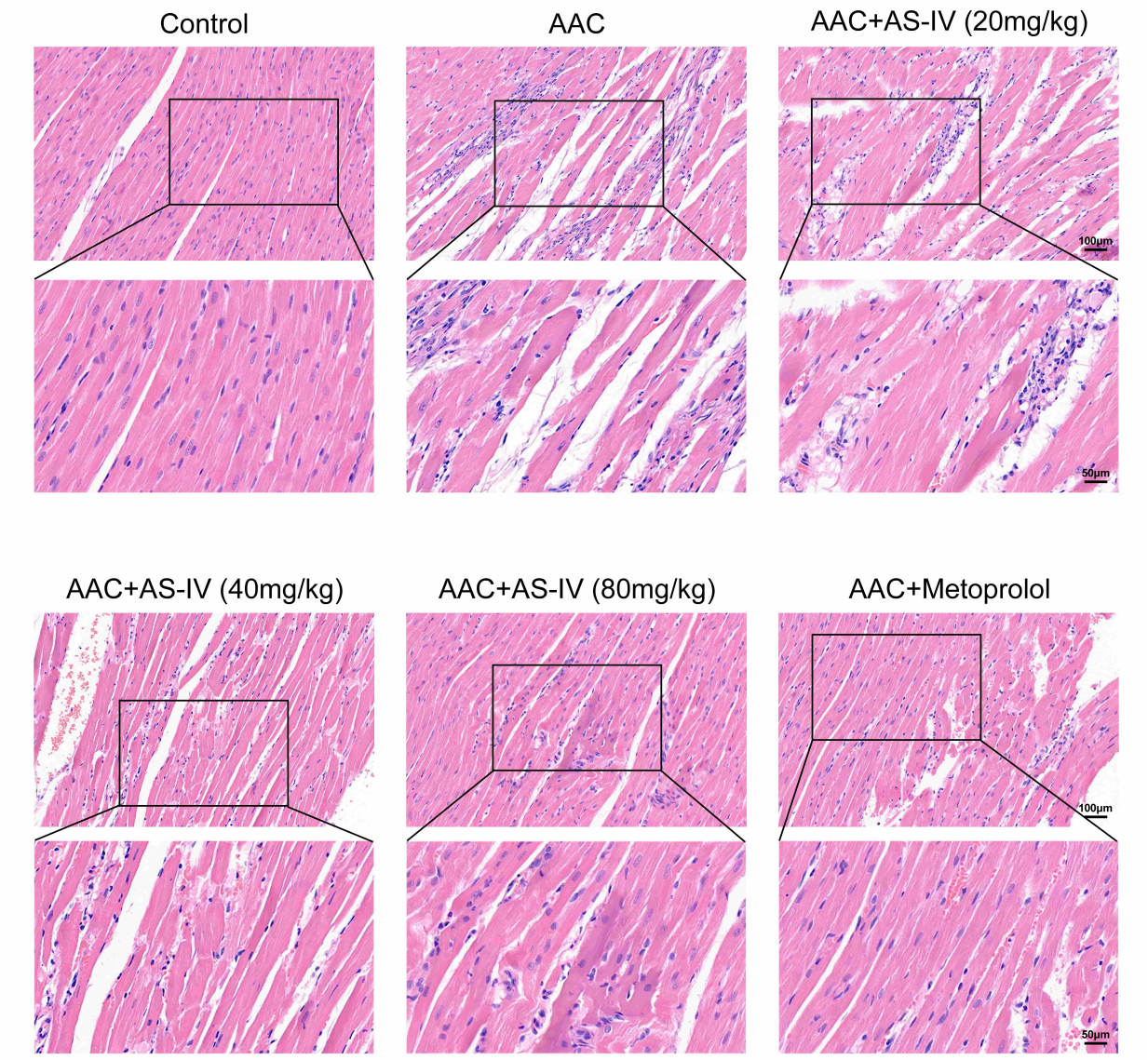

FIGURE 3. Astragaloside IV alleviated myocardial injury. Groups were separated into the Control, AAC, AAC + AS-IV (20 mg/kg), AAC + AS-IV (40 mg/kg), AAC + AS-IV (80 mg/kg) and AAC + Metoprolol groups. The pathological changes of myocardial tissues were assessed through HE staining. AAC: Abdominal aorta coarctation; AS-IV: Astragaloside IV.

[18]. Furthermore, an abrupt rise in plasma free fatty acid (FFA) concentration can inhibit glucose absorption and impair insulin signaling, ultimately promoting insulin resistance [19]. Furthermore, inflammation within fat tissues can lead to insulin resistance throughout the body [20]. In this study, it was demonstrated that AS-IV reduced HOMA-IR value, indicating that AS-IV improved insulin resistance. In addition, it was verified that AS-IV can alleviate inflammation.

The inactivation of p38 pathway and activation of Akt pathway play pivotal roles with many heart diseases, including heart failure [21, 22]. Of significance is the elevated p38 phosphorylation observed in the hearts of individuals with insulin resistance, which in turn accelerates insulin resistance by inhibiting the chronic insulin signaling mediated by IRS1 and IRS2 [23]. Additionally, Hirsutine has the ability to activate the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, enhancing glucose consumption and uptake in a cardiac insulin-resistant cell model [24]. Interestingly, AS-IV retards the p38 pathway to restore cardiac function [25]. Nevertheless, further investigations are required to understand the regulatory effects of AS-IV on the p38 pathway in heart failure associated with insulin resistance. The study demonstrated that AS-IV inhibited the p38 pathway while promoting the Akt pathway both in *in vivo* and *in vitro* experiments.

5. Conclusions

In conclusion, it was disclosed that AS-IV can improve myocardial injury, as well as modulate the p38 and Akt pathways in insulin-resistant heart failure *in vitro* and *in vivo*. Nevertheless, this study is not without its limitations. These include the challenge of translating findings from the animal model to human cases of insulin-resistant heart failure and the absence of clinical investigations. Moving forward, further experiments will be conducted to explore additional regulatory effects of AS-IV in the context of insulin-resistant heart failure.

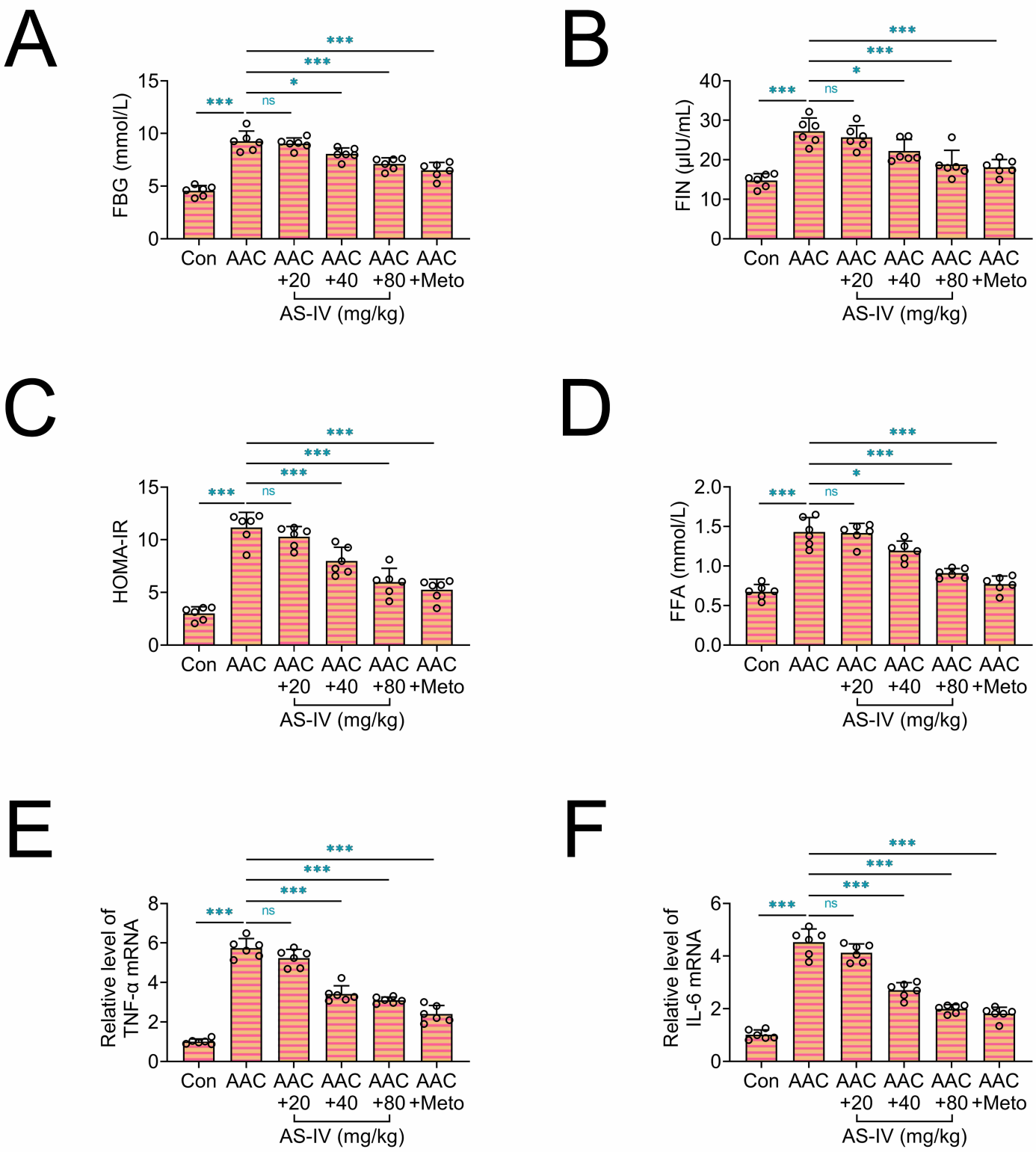

FIGURE 4. Astragaloside IV affected insulin-resistant. Groups were separated into the Control, AAC, AAC + AS-IV (20 mg/kg), AAC + AS-IV (40 mg/kg), AAC + AS-IV (80 mg/kg) and AAC + Metoprolol groups. (A) The fasting blood glucose (FBG) was evaluated through the blood glucose meter. (B) The fasting insulin (FIN) was measured by the FIN kit. (C) The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. (D) Serum free fatty acid (FFA) was determined using the commercial kit. (E,F) The mRNA expressions of TNF-α and IL-6 in serum were tested through RT-qPCR. *$p < 0.05$, ***$p < 0.001$. AAC: Abdominal aorta coarctation; AS-IV: Astragaloside IV; Con: Control; AAC: Abdominal aorta coarctation; Meto: Metoprolol; TNF-α: Tumor Necrosis Factor-α; IL-6: Interleukin 6; ns: no significance.

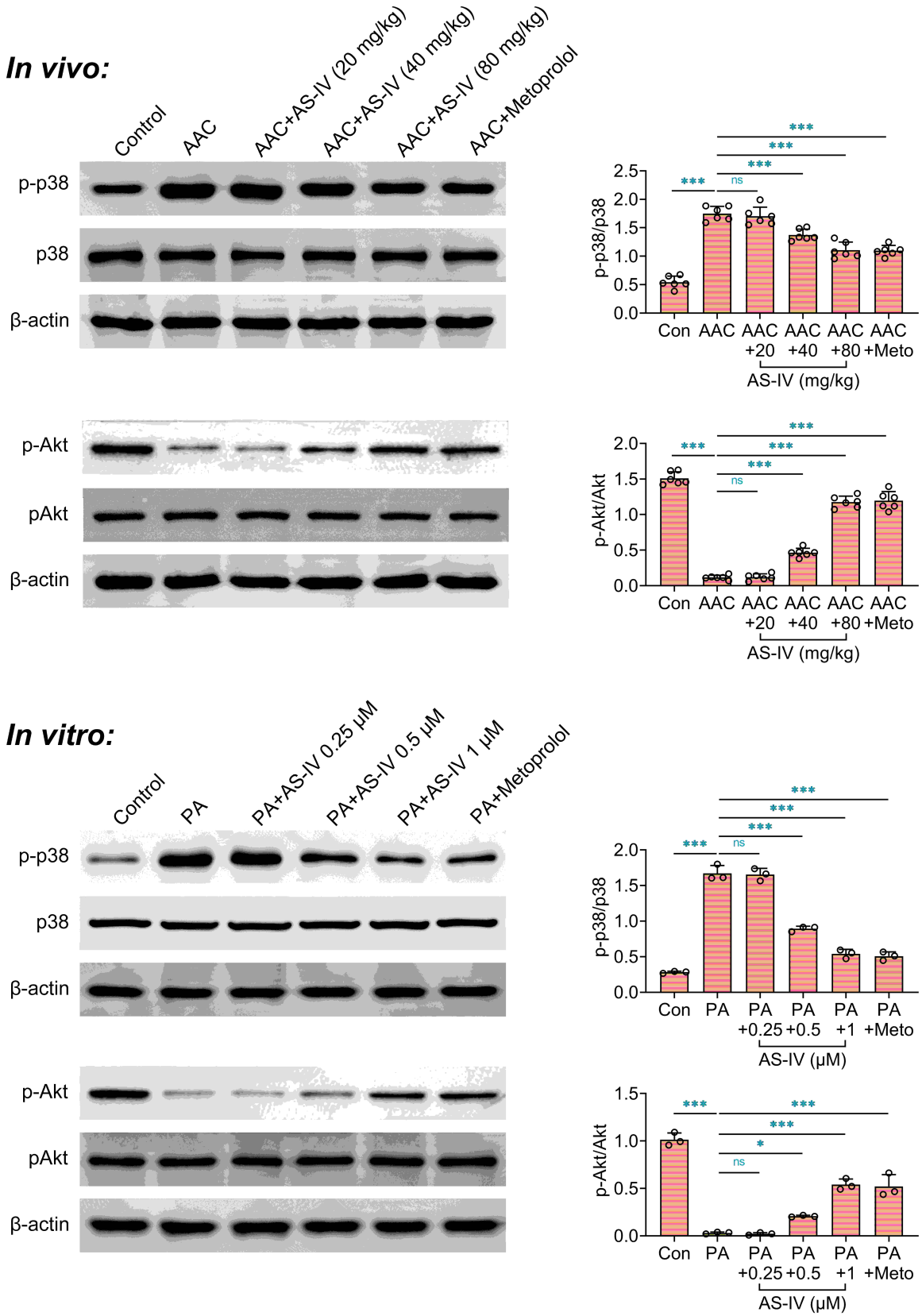

FIGURE 5. Astragaloside IV regulated the p38 pathway. Groups were separated into the Control, AAC, AAC + AS-IV (20 mg/kg), AAC + AS-IV (40 mg/kg), AAC + AS-IV (80 mg/kg) and AAC + Metoprolol groups. The protein expressions of p-p38, p38, p-Akt and Akt were determined through western blot. Groups were separated into the Control, PA, PA + AS-IV 0.25 μM, PA + AS-IV 0.5 μM, PA + AS-IV 1 μM and PA + Metoprolol groups. The protein expressions of p-p38, p38, p-Akt and Akt were inspected through western blot. *$p < 0.05$, ***$p < 0.001$. AAC: Abdominal aorta coarctation; AS-IV: Astragaloside IV; PA: almitic acid; ns: no significance; Akt: protein kinase B.

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

YYW—designed the study and carried them out; YYW, YJC, TXL, PZ—supervised the data collection; YYW, YJC, TXL, PZ—analyzed the data, analyzed the data; YYW, YJC, TXL, QSW—interpreted the data; YYW, YJC—prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Experimental Animal Ethics Review Committee, Guizhou University of Traditional Chinese Medicine (Approval no. 20240510001).

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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