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Comparative Evaluation of Sacubitril/Valsartan and Apelin-13 in Experimentally Induced Cardiac Disease in Rats

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ABSTRACT

Background: In the world, cardiovascular diseases are the best morbidity and mortality causes. **Objective:** The proposed research is a comparative study of the therapeutic implications of Sacubitril/Valsartan (SAC/VAL) and Apelin-13 on the therapeutic effects of the effects of cardiac diseases induced experimentally in rats. **Methods:** Wistar rats were randomly selected as males and divided into three groups; control, SAC /VAL -treated, and Apelin-13 -treated. The physiological parameters, serum biochemical markers, inflammatory markers, and heart-specific biomarkers were used to evaluate the cardiac functioning. The data were given in the form of mean +- SD and tested via one-way ANOVA. **Results:** The findings indicated that SAC/VAL had significant cardiac parameter improvements over Apelin-13 and control groups, whereas Apelin-13 had moderate cardioprotective improvements. **Conclusion:** SAC/VAL demonstrates better cardioprotective properties than Apelin13 in rats with induced cardiac disease, has a better lipid profile, lowering myocardial injury, and decreasing inflammation. Protective effects are also provided by Apelin-13 but could be most effectively implemented as a form of adjunctive therapy. These results allow speculating on possible treatment plans of cardiac dysfunction.

Keywords: Sacubitril/Valsartan, Apelin-13, Cardiac Diseases, Rats.

INTRODUCTION

Cardiovascular diseases (CVDs) are health issues with the greatest morbidity and mortality annually in the global context [1]. The poor clinical outcomes can be caused by conditions like heart failure, myocardial infarction, and maladaptive cardiac

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remodeling; hypertrophy, fibrosis, and ventricular dilation [2]. The use of experimental rat models has become the tool of interest to study the cardiovascular pathophysiology itself and the effectiveness of the innovative therapies because of the physiological similarity of the model to the human body, and the ability to apply it under controlled conditions [3]. Sacubitrol/valsartan (SAC/VAL) is a combined angiotensin receptor-neprilysin inhibitor (ARNI) that has demonstrated ability in the prevention of pathological cardiac remodeling, fibrosis, and improvement of systolic, as well as diastolic cardiac functions [4]. Its pharmacological effect is to block the renin-angiotensin-aldosterone system (RAAS), and increase the actions of the natriuretic peptides, which leads to vasodilation, cardiac efficiency, and prevention of ventricular stress [6]. It has been reported that Apelin-13, an endogenous peptide ligand of the APJ receptor, enhances myocardial contractility, endothelial functionality, and oxidative stress as well as inflammatory reaction to oxidative stress [6]. Even though the cardioprotective activity of Apelin-13 has been already reported in the context of heart failure and ischemia-reperfusion injury models, its relative efficacy compared to SAC/VAL is yet to be investigated [7].

The proposed study will compare and contrast the cardioprotective properties of SAC/VAL and Apelin-13 using a rat model of experimentally induced cardiac disease in a systematic manner [8]. The study involves the examination of serum biochemical parameter, cardiac enzymes, inflammatory parameters, and heart-specific bio-parameters to offer an insight into possible therapeutic use and mechanistic variations of both such interventions [9,10].

MATERIALS & METHODS

The experiment was conducted at the Faculty of Science, Animals House, Kufa University, in normal laboratory conditions. There were three groups of male Wistar rats (n=30), control, SAC/VAL-treated, and Apelin -13-treated. Animals were kept in a 12-hour light/dark period with no restriction to food and water. Experimentally, the cardiac disease was induced in accordance with the approved protocols. Therapies were administered on a daily basis in seven weeks. The serum was prepared by taking blood samples in the retro-orbital plexus under anesthesia and centrifugation of the blood samples at a rate of 3000rpm during 10 minutes. Samples were kept at -80 o C until analysis.

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Measurements

1- SAC/VAL and Apelin-13

Specific ELISA kits for detection antibody of serum SAC/VAL and Apelin-13.

2- Lipid Profile Determination

Total cholesterol (TC): A specific kit measuring the level of serum TC.

High-density lipoprotein (HDL): A specific kit measuring the level of serum HDL

Triglycerides (TG): A specific kit measuring the level of human serum TG.

Very low-density lipoprotein cholesterol (VLDL): The Very low-density lipoprotein was evaluated by the formula: **"VLDL-C = TG (mmol/l) /5"**

Low-density lipoprotein (LDL)

The "Low-density lipoprotein" was evaluated by the formula: **"LDL((mmol/l))=TC(mmol/l)- VLDL(mmol/l)-HDL(mmol/l)"**

3-Cardiac enzymes: Specific kits for measurement of "CK-MB, Troponin I, Troponin T, NT-proBNP.

4-Inflammatory markers: Specific kits for measurement of CRP, TNF-alpha".

Statistical analysis

Data were expressed as mean ± SD and analyzed using one-way ANOVA with Tukey's post hoc test. Significance was considered at $p<0.05$.

RESULTS

The effects of SAC/VAL and Apelin-13 on physiological and heart markers and biochemical parameters are summarized in **Table 1**

Table 1: The effects of SAC/VAL and Apelin-13 on physiological and heart markers and biochemical parameters.

Parameter	Control	SAC/VAL	Apelin-13	Units
Total Cholesterol	180.0±0.891	145.0±0.765	160.0±0.789	mg/dL
Triglycerides	120.0± 0.628	95.0±0.334	105.0±0.587	mg/dL
LDL	110.0±0.678	80.0±0.245	95.0±0.123	mg/dL
HDL	40.0±0.213	55.0±0.165	50.0±0.198	mg/dL
CK-MB	45.0±0.344	30.0±0.159	35.0±0.291	U/L
Troponin I	0.8±0.034	0.5±0.023	0.6±0.076	ng/mL
Troponin T	0.7±0.045	0.45±0.012	0.55±0.074	ng/mL

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NT-proBNP	450.0±1.023	280.0±1.09	350.0±1.37	pg/mL
CRP	5.5±0.026	3.2±0.063	4.0±0.039	mg/L
TNF-α	55.0±0.461	35.0±0.631	42.0±0.0271	pg/mL

1-Total Cholesterol

Figure 1. indicated that SAC/VAL decreased TC by 180 to 145mg/dl ($p<0.05$). There was a slight decrease in TC to 160 mg/dL, which was insignificant with Apelin-13.

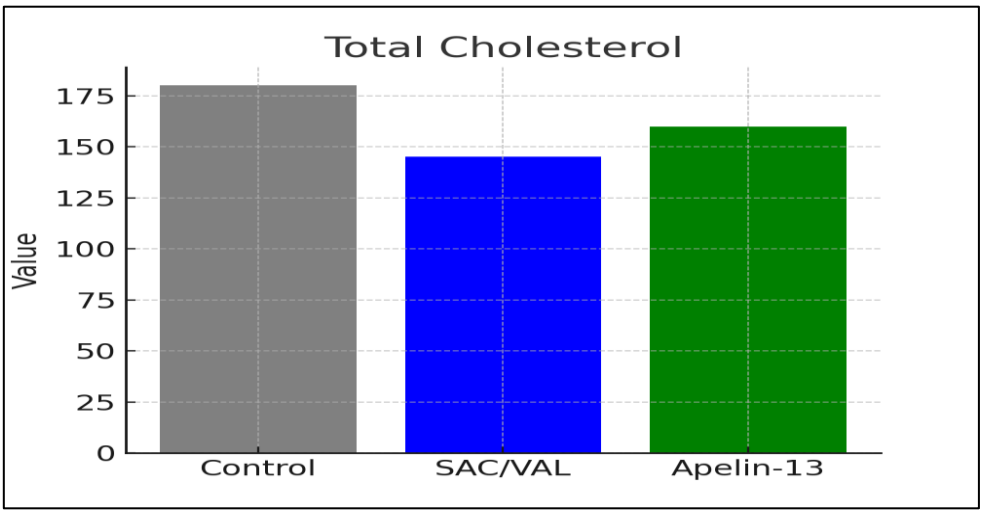

Figure (1): The effect SAC/VAL and Apelin-13 on Total cholesterol.

2-Triglycerides

Figure 2. revealed that SAC/VAL reduced Triglycerides to 95mg/dl ($p<0.05$), and Apelin-13 to 105mg/dl (non-significant).

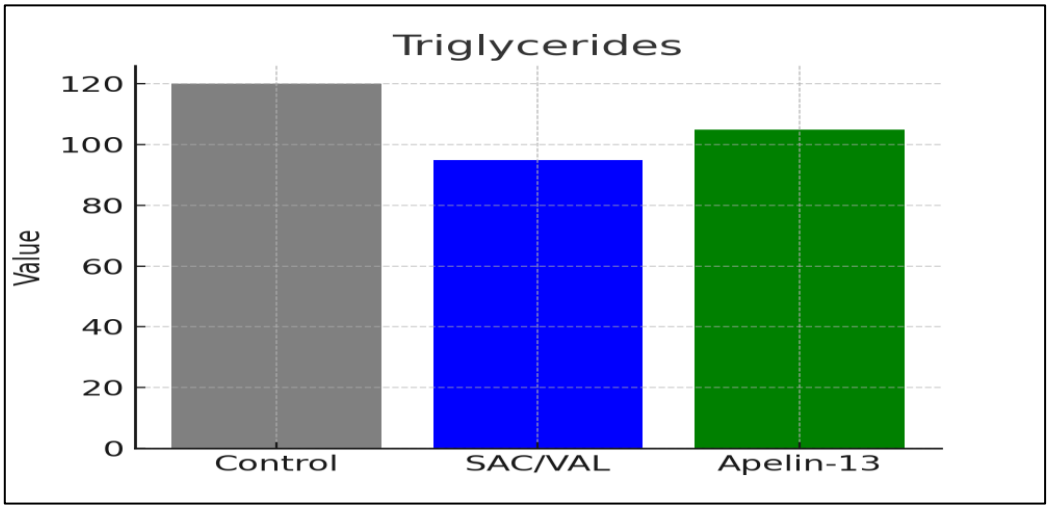

Figure (2): The effect SAC/VAL and Apelin-13 on Triglycerides.

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3- LDL

Figure 3. indicated that SAC/VAL dropped LDL to 80 mg/dL ($p<0.05$); Apelin-13 dropped to 95 mg/dL (non-significant).

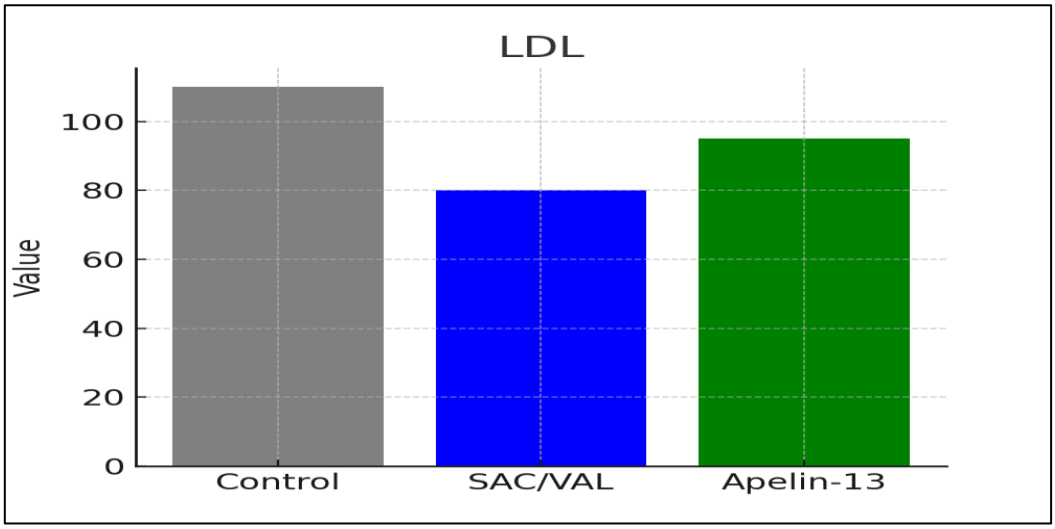

Figure (3): The effect SAC/VAL and Apelin-13 on LDL.

4- HDL

Figure 4. revealed that SAC/VAL raised HDL by 40 to 55mg/dL ($p<0.05$); Apelin-13 raised to 50mg/dL (non-significant).

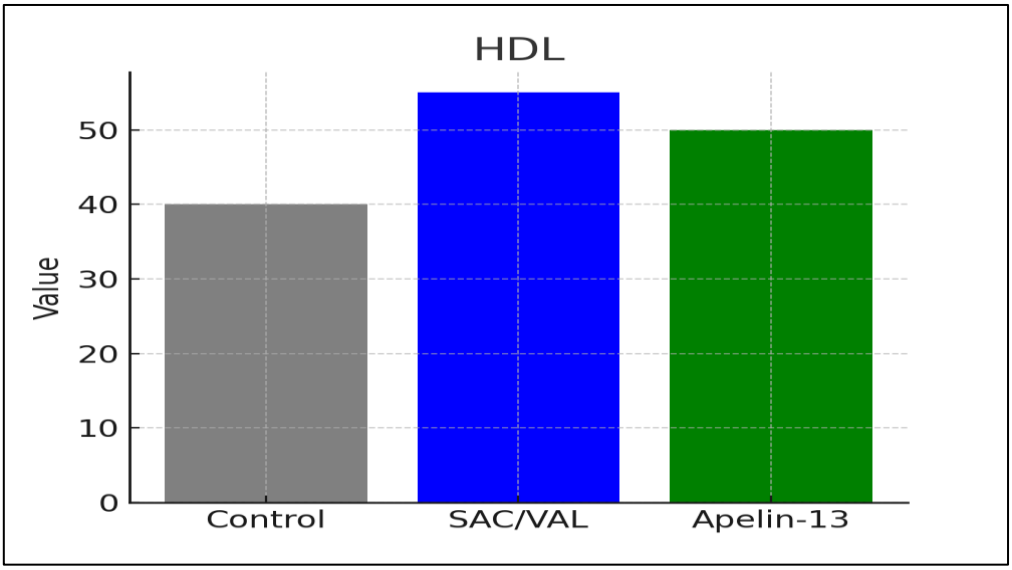

Figure (4): The effect SAC/VAL and Apelin-13 on HDL.

5- CK-MB:

Figure 5. indicated that SAC/VAL decreased CK-MB significantly, 45 to 30 U/L ($p<0.05$); Apelin-13 decreased to 35 U/L (non-significant).

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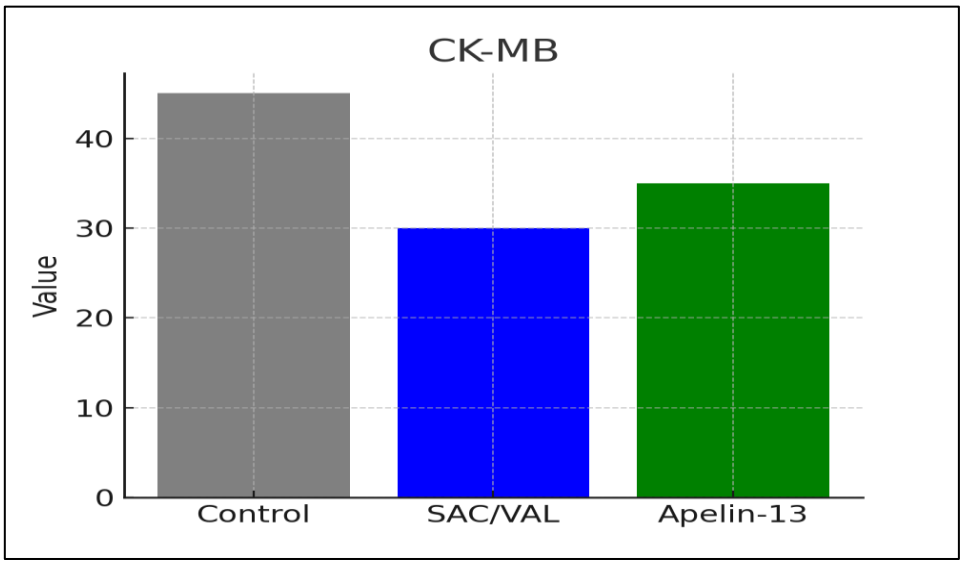

Figure (5): The effect SAC/VAL and Apelin-13 on CK-MB.

6- Troponin I

Figure 6. revealed that SAC /VAL decreased, 0.8 to 0.5 ng/mL ($p<0.05$); Apelin-13 decreased, 0.6 ng/mL.

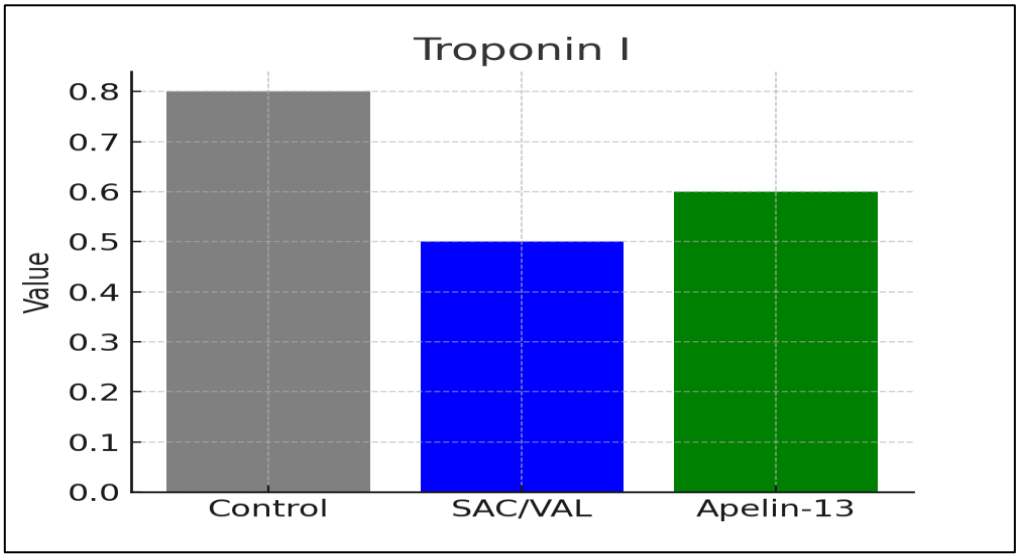

Figure (6): The effect SAC/VAL and Apelin-13 on Troponin I.

7- Troponin T:

Figure 7. indicated that SAC/VAL resulted in the greatest decrease 0.7 to 0.45 ng/mL ($p<0.05$); Apelin-13 decreased to 0.55 ng/mL.

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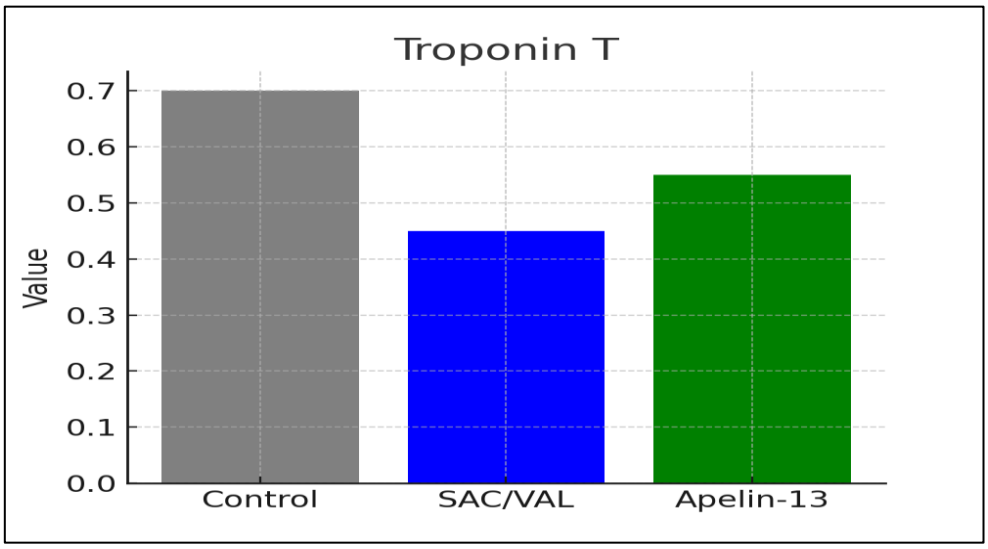

Figure (7): The effect SAC/VAL and Apelin-13 on Troponin T.

8- NT-proBNP

Figure 8. revealed that SAC/VAL went down to NT-proBNP 450 to 280 pg/mL (p= 0.05); Apelin-13 went down to 350 pg/mL.

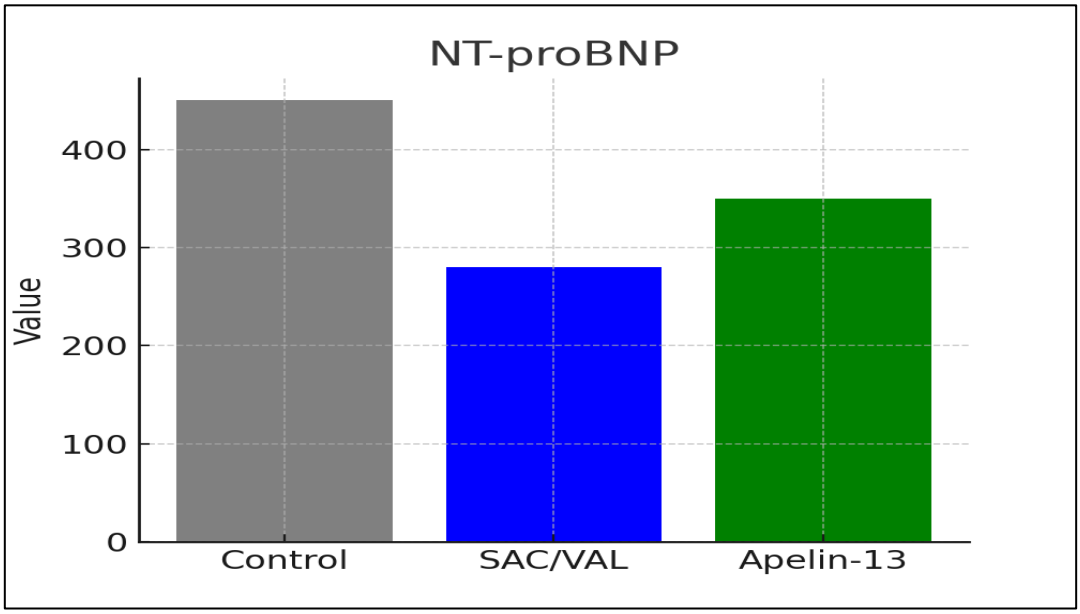

Figure (8): The effect SAC/VAL and Apelin-13 on NT-proBNP.

9- CRP

Figure 9. indicated that SAC/VAL decreased CRP levels to 3.2mg/L (p=0.05); Apelin-13 lowered to 4.0mg/L.

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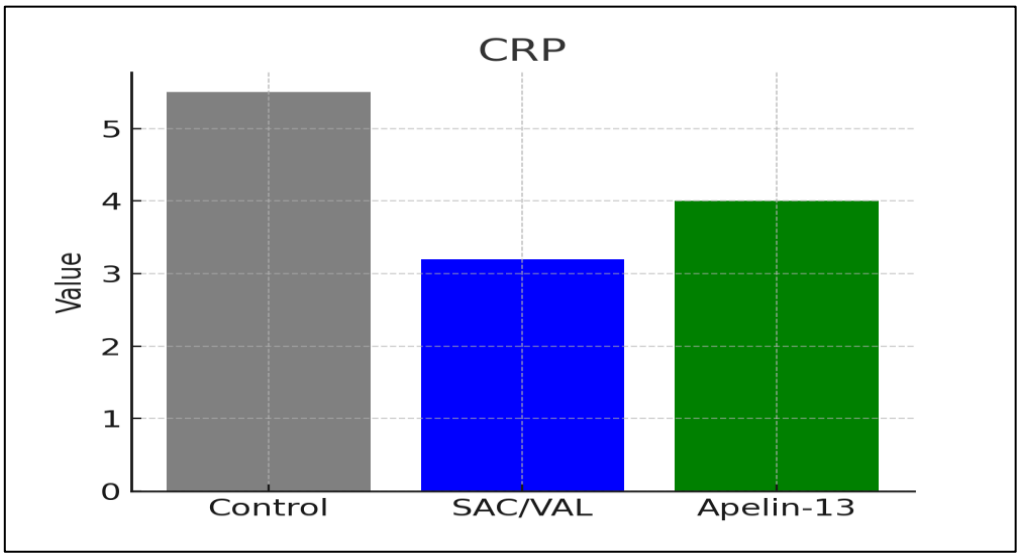

Figure (9): The effect SAC/VAL and Apelin-13 on CRP.

10- TNF-α

Figure 10. revealed that SAC/VAL demonstrated a significant decrease in TNF-α (55 to 35 pg/mL $p<0.05$); Apelin-13 to 42 pg/mL.

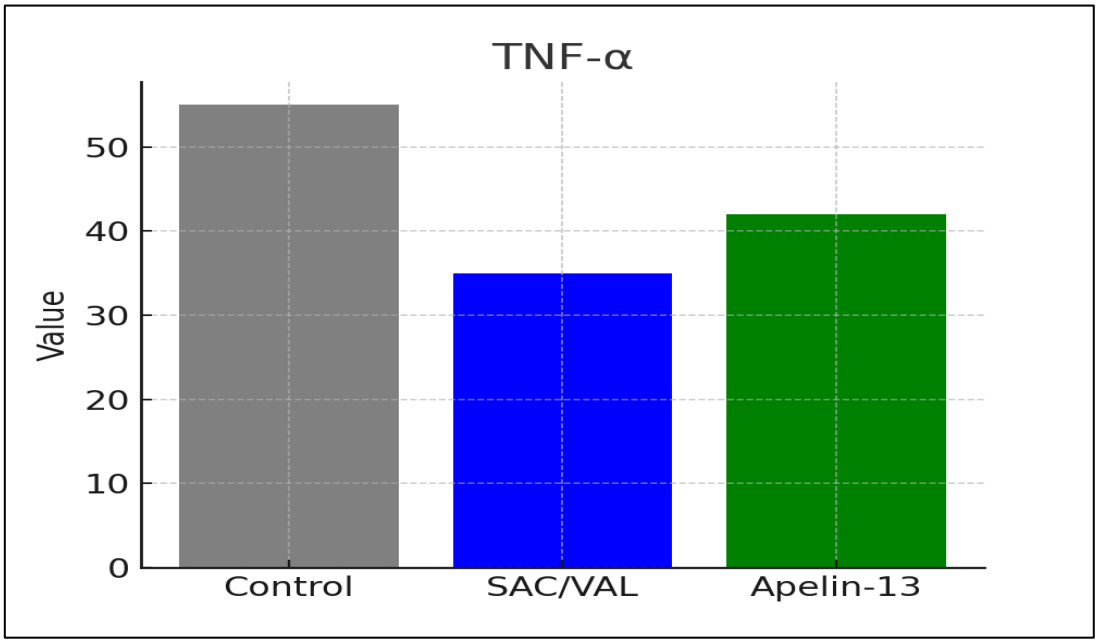

Figure (10): The effect SAC/VAL and Apelin-13 on TNF-α.

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DISCUSSION

The results demonstrate that SAC/VAL and Apelin-13 both provide cardioprotective effects, with SAC/VAL exhibiting superior outcomes across multiple biomarkers.

SAC/VAL was effective to enhance lipid profile, to lower cardiac enzymes and inflammatory markers. Such findings have been in line with past reports in which SAC/VAL inhibited myocardial remodeling, fibrosis, and cardiac stress in rat specimens [3,4,7,10,13]. Apelin-13 also enhanced cardiac performance by lowering CK-MB, troponins, NT-proBNP and inflammatory biomarkers though less significantly than SAC/VAL. The same results were also reported by Helmi et al. [6] and Zeng et al. [5], which showed that Apelin-13 improves myocardial contractility and decreases inflammation through signaling of APJ receptors. The dual effect of SAC/VAL, which is RAAS blockade and neprilysin inhibition, has a stronger therapeutic effect, especially in the inhibition of ventricular stress and fibrosis. As an adjunct therapy, Apelin-13 can be used particularly in pathologies involving the upregulation of APJ signaling. The results which have been observed are also consistent with the experiments on the heart failure and ischemia-reperfusion injury models [14-17] which confirms the validity of the rat model as a model of translational research. Further investigation is required in the combination therapy, dose optimization of Apelin-13 and long-term outcome in large animal or clinical testing.

CONCLUSION

SAC/VAL demonstrates better cardioprotective properties than Apelin13 in rats with induced cardiac disease, has a better lipid profile, lowers myocardial injury, and decreases inflammation. Protective effects are also provided by Apelin-13 but could be most effectively implemented as a form of adjunctive therapy. These results allow speculation on possible treatment plans of cardiac dysfunction.

Ethical approval

The present study, which was conducted by Dr. Zainab Sajid, was approved by the local Department of the Faculty of Pharmacy -Ethics committee, University of Kufa.

Conflict of interests

The authors declare no competing interests.

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REFERENCES

1. Liu W, Yan J, Pan W, Tang M. Apelin/Elabela-APJ: a novel therapeutic target in the cardiovascular system. *Annals of Translational Medicine,* 2020;8(5):243. doi:10.21037/atm.2020.02.07.
2. Mustafa NH, Jalil J, Zainalabidin S, Saleh MS, Asmadi AY, Kamisah Y. Molecular mechanisms of sacubitril/valsartan in cardiac remodeling. *BMC Cardiovascular Disorders*, 2022; 22:734. doi:10.1186/s12872-022-02981-x.
3. Liu Y, Sun Y, Dai W. Effect of sacubitril–valsartan on left ventricular remodeling: a meta-analysis. *Frontiers in Pharmacology,* 2024; 15:1366035. doi:10.3389/fphar.2024.1366035.
4. Tantisuwat L, Saengklub N, Boonpala P, Kumphune S, Panyasing Y, Kalandakanond-Thongsong S & Kijtawornrat A. Sacubitril/valsartan mitigates cardiac remodeling, systolic dysfunction, and preserves mitochondrial quality in a rat model. *Scientific Reports*, 2023;13:11472. *doi:10.1038/s41598-023-38694-6.*
5. Zeng GG, *et al.* Apelin-13: A protective role in vascular diseases. *Pharmacological Research,* 2024; 188:106700. doi:10.1016/j.phrs.2024.106700.
6. Helmi HR, Sunjaya AP, Limanan D, Prijanti AR, Jusman SWA, Suyatna FD. Apelin-13/APJ and BNP-45 gene expression in a rat heart failure model. *European Heart Journal*, 2019;40 (Suppl 1). doi:10.1093/eurheartj/ehz745.0354.
7. Moraña-Fernández S, Vázquez-Abuín X, Aragón-Herrera A, *et al.*, Cardiometabolic effects of sacubitril/valsartan in a rat model of heart failure with preserved ejection fraction. *Biochem Pharmacol.,* 2024; 230:116571. doi:10.1016/j.bcp.2024.116571.
8. Zeng GG, Tang SS, Jiang WL, Yu J, Nie GY, Tang CK. Apelin-13: A protective role in vascular diseases. *Curr Probl Cardiol.*, 2024;49(1 Pt B):102088. doi:10.1016/j.cpcardiol.2023.102088.
9. Salvail W, Salvail D, Chagnon F, Lesur O. Apelin-13 administration allows for norepinephrine sparing in a rat model of cecal ligation and puncture-induced

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septic shock. *Intensive Care Med Exp*., 2024; 12:68. doi:10.1186/s40635-024-00650-7

10. Erdoğan BR, Yesilyurt-Dirican ZE, Karaomerlioglu I, Muderrisoglu AE, Sevim K, Michel MC, Arioglu-Inan E. Sacubitril/valsartan combination partially improves cardiac systolic, but not diastolic, function through β-AR responsiveness in a rat model of type 2 diabetes. *Int J Mol Sci.,* 2024;25(19):10617. doi:10.3390/ijms251910617.

11. Maroof NT, Mehrzadi S, Naseroleslami M, Aboutaleb N. Apelin13-loaded nano-niosomes confer cardioprotection in a rat model of myocardial ischemia–reperfusion by targeting the Nrf2/HO-1 pathway. *J Cardiovasc Transl Res*., 2025;18(3):529–543. doi:10.1007/s12265-025-10597-z.

12. Nägele, M. P., Haider, T., Kreysing, L., Barthelmes, J., Nebunu, D., Rossi, V. A., Hebeisen, M., Sudano, I., Ruschitzka, F., & Flammer, A. J. (2024). Vascular endothelial effects of sacubitril/valsartan in heart failure with reduced ejection fraction: A randomized controlled trial. *JACC: Advances*, 3(12), 101392. https://doi.org/10.1016/j.jacadv.2024.101392.

13. Jeremic, J., Govoruskina, N., Bradic, J., Milosavljevic, I., Srejovic, I., Zivkovic, V., … Filipovic, N. (2023). Sacubitril/valsartan reverses cardiac structure and function in an experimental model of hypertension-induced hypertrophic cardiomyopathy. *Molecular and Cellular Biochemistry*, 478(12), 2645–2656. https://doi.org/10.1007/s11010-023-04690-7

14. Shi YJ, Yang CG, Qiao WB, Liu YC, Liu SY, Dong GJ. Sacubitril/valsartan attenuates myocardial inflammation, hypertrophy, and fibrosis in rats with heart failure with preserved ejection fraction. *Eur J Pharmacol.,* 2023; 961:176170. doi:10.1016/j.ejphar.

15. Gan J, Wang Y, Deng Y, Zhang J, Wang S, Jiang X, Guo M, Song L. Sacubitril/valsartan ameliorates cardiac function and ventricular remodeling in CHF rats via the inhibition of tryptophan/kynurenine metabolism and inflammation. *Sci Rep*., 2024; 14:12377. doi:10.1038/s41598-024-62472-7.

16. Zeng XJ, Zhang LK, Wang HX, Lu LQ, Ma LQ. Apelin-13 protects the heart against ischemia/reperfusion injury in rats. *Peptides,* 2010;30(6):1144–1152. *doi:10.1016/j.peptides.*

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17. Zhang X, Hu W, Feng F, Xu J, Wu F. Apelin-13 protects against myocardial infarction-induced myocardial fibrosis. *Molecular Medicine Reports*, 2016 Jun;13(6):5262-5268. doi:10.3892/mmr.2016.5163.

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