



# L-arginine attenuates downregulated SERCA2a activity via enhanced PI3K/VEGF signalling in monosodium glutamate-induced cardiac toxicity of male Wistar rats

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## ABSTRACT

L-arginine is a semi-essential amino acid that is produced endogenously and can be obtained through dietary supplements. Monosodium glutamate (MSG) is an umami flavor enhancer used in packaged and processed food and has been associated with cardiotoxicity and inflammation. The sarcoplasmic/endoplasmic reticulum Ca<sup>2+</sup>-ATPase 2a (SERCA2a) is a key player in the Ca<sup>2+</sup> cycle of cardiac regulation. This study aims to evaluate the effect of L-arginine on SERCA2a in MSG-induced cardiac toxicity.

Twenty male Wistar rats weighing 100–120 g were divided into four groups ( $n = 5/\text{group}$ ) and were fed as group 1; control- rat chow + olive oil (vehicle); group 2; rat chow+ L-arginine (150 mg/kg), group 3; MSG (120 mg/kg) + vehicle, group 4; MSG+ L-Arginine daily for 6 weeks respectively. At the end of the experiment, rats were anaesthetized with 0.3 ml of 1.M ketamine hydrochloride (50mg/ml), and blood was collected by cardiac puncture. Serum and cardiac tissue homogenate were analyzed, and values expressed as mean  $\pm$  SEM with  $p$ -values  $< 0.05$  accepted as significant.

The results showed that MSG, compared with the control, significantly decreased plasma and cardiac NO, NADPH, GPx, Ca<sup>2+</sup>, cardiac SERCA2a activity, VEGF, and PI3K, and increased plasma and cardiac MDA and uric acid ( $P < 0.05$ ). However, L-arginine significantly increased NO, NADPH, GPx, and cardiac SERCA2a activity, as well as VEGF and PI3K, compared with the control and MSG-treated groups.

In conclusion, L-arginine attenuated MSG-induced cardiotoxicity by restoring calcium handling and redox balance, as well as modulating VEGF-PI3K/Akt survival signaling to reduce apoptotic and metabolic dysfunctions.

## Introduction

Cardiovascular diseases are the most prevalent noncommunicable diseases worldwide, responsible for about one-third of all deaths [1]. Cardiotoxicity, characterized by impaired cardiac function, increases cardiovascular risk [2]. In addition to conventional factors such as obesity, hypertension, dyslipidemia, and diabetes [3], dietary components like excessive monosodium glutamate (MSG) may further aggravate cardiovascular risk by promoting obesity, hypertension, dyslipidemia, and metabolic disturbances [4,5].

MSG, a sodium salt of glutamic acid widely used as a flavor enhancer, is recognized as safe by regulatory agencies such as the U.S. FDA [6]. However, experimental evidence implicates excessive MSG in cardiotoxicity, mediated primarily through oxidative stress and calcium dysregulation [7,8]. Calcium overload disrupts mitochondrial function, elevates reactive oxygen species, and activates apoptotic pathways, impairing cardiac contractility and function.

Calcium regulation is critical for cardiac excitation-contraction coupling, with sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase 2a (SERCA2a) ensuring efficient reuptake of cytosolic calcium into the sarcoplasmic

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reticulum [9]. Oxidative stress can impair these calcium-handling proteins, reinforcing cardiac dysfunction [10,11]. Dysfunction of SERCA2a results in abnormal calcium cycling and reduced contractility, a hallmark of heart failure, and represents a promising therapeutic target [12, 13]. Hence the need to explore potential nutritional supplements of immense cardiovascular benefits.

L-arginine, a semi-essential amino acid and substrate for nitric oxide (NO) production, supports vascular tone, endothelial function, and cardioprotection [14–16]. Beyond vasodilation, L-arginine enhances SERCA2a activity through NO signaling, restoring calcium cycling and reducing oxidative stress [17].

Growth factor signaling also contributes to cardiac survival responses, and VEGF–PI3K/Akt signaling regulates apoptosis and interacts with calcium handling via SERCA2a activity [18,19]. Under oxidative stress, disturbances in this pathway may tip the balance toward apoptosis [20].

This study, therefore, investigates the effect of L-arginine on SERCA2a and vascular activity via a downstream regulating receptor, in MSG-induced cardiac toxicity in Male Wistar rats.

## Materials and methods

### 2.1. Ethics statement

The experiment was performed in accordance with the National Institute of Health (NIH) guidelines for the care and use of laboratory animals. The experimental protocol was approved by the Faculty of Basic Medical Sciences, University of Ilorin Ethical Review Committee and Institutional Review Board of the University of Ilorin, with protocol identification number UERC/ASN/2020/357. This study adhered to the guidelines established by the National Institutes of Health for the Care and Use of Laboratory Animals, and all efforts were made to reduce both the number of animals used and their suffering. The study design also adhered to standard guidelines, ensuring a robust and reproducible approach. To minimize bias, the blood samples were numbered 1 to 20 without any indication of grouping. This blinding method ensured that the analysis was conducted objectively, and outcome measures were clearly defined and reported following accurate analysis and interpretation of data.

### 2.2. Animal grouping and treatment

Twenty male Wistar rats with a mean weight of  $110 \pm 10$  g obtained from the animal house of the Department of Physiology, University of Ilorin, Ilorin, were divided into four groups ( $n = 5$ /group) after a week of acclimatization. The rats were treated respectively as control- rat chow + olive oil (vehicle); group 2; rat chow+ L-arginine (150 mg/kg), group 3; MSG (120 mg/kg) + vehicle, group 4; MSG+ L-Arginine daily for 6 weeks. At the end of the experiment, rats were anaesthetized with 0.3 ml of 1.M ketamine hydrochloride (50mg/ml), and blood was collected by cardiac puncture. Throughout the experiment, the animals were provided with unlimited access to standard rat chow, clean water, and kept under standard housing conditions.

### 2.3. Collection of blood samples and cardiac homogenates

Blood was collected by cardiac puncture and centrifuged at 3000 rpm for 5 min at room temperature. Serum was collected into a well-labeled plain bottle and kept frozen until it was time for the biochemical assay. The heart was removed after dissection, cleaned of adherent connective tissues, blotted, and weighed, and 100 mg of the tissue was homogenized in phosphate-buffered solution (PBS) and centrifuged at 10,000 rpm for 10 min at 4 °C.

### 2.4. Monosodium glutamate and L-arginine

Analytical and pure monosodium glutamate (MSG) weighing 5 kg was purchased from Bridge Biotech Laboratory, Ilorin, Kwara State, and was given at a dose of 120 mg/kg per day for the period of six weeks [21]. L-arginine was also purchased from the same laboratory. The L-arginine was dissolved in distilled water. It was prepared freshly and administered orally at a dose of 150 mg/kg [22] body weight for a period of six weeks.

### 2.5. Biochemical assay

SERCA2a analysis was done using commercial assay kits purchased from Elabscience®, USA, with Cat no: ELK7804, and serum and tissue homogenates were analyzed following the manufacturer's instructions. Post-excision, the heart was homogenized in cold SERCA2a assay buffer (typically containing 50 mM Tris–HCl, 5 mM MgCl<sub>2</sub>, and 0.1 mM CaCl<sub>2</sub>, pH 7.4) following same homogenate centrifugation and the supernatant was collected and stored at –80 °C. SERCA2a activity was assessed using a commercial colorimetric SERCA2a assay kit, which measures the rate of ATP hydrolysis linked to Ca<sup>2+</sup> uptake. The assay was carried out according to the manufacturer's protocol and absorbance was read at 660 nm using a spectrophotometer.

Phosphatidylinositol 3-kinase (also known as PI3K) assay was done using the Sandwich-ELISA kit purchased from Elabscience® with Cat no: E0438Ra, following the manufacturer's protocol.

The Sandwich-ELISA kit from Elabscience® (cat number: Rat VEGF-A: E-EL-R2603) was used for the vascular endothelial growth factor (VEGF) assay according to the manufacturer's instructions.

Glucose-6-phosphate dehydrogenase (G6PD) and NADPH activity were determined using standard enzymatic and non-enzymatic spectrophotometric methods, respectively, with assay kits obtained from Oxford Biomedical Research Inc. (Oxford, USA). The G6PD activity spectrophotometric determination is based on the evaluation of absorbance at 340 nm given by NADPH formation; the quantitative evaluation is made by adding a precise amount of enzyme solution to an assay mixture containing the substrate (glucose-6-phosphate) and its cofactor NADP and the rate of NADPH generation is spectrophotometrically measured at a wavelength of 340 nm [23].

GPx activity was measured using an enzymatic assay kit (Fortress Diagnostics Limited, UK) following the manufacturer's instructions. It is based on the oxidation of reduced glutathione by the sample GPx. The oxidised glutathione is then reduced by the action of glutathione reductase and NADPH. In the reaction, 1unit GPx causes the formation of 1.0 mmol of NADP<sup>+</sup> from NADPH per minute. Thus, GPx enzyme activity was calculated as units per mg of sample protein concentration.

Also, malondialdehyde (MDA), nitric oxide, and serum calcium, after being collected in appropriate sample bottles, were measured using standardized colorimetric methods and an assay kit obtained from Randox Laboratory Ltd. (Co. Antrim, UK).

### 2.6. Statistical analysis

The data were presented as Mean  $\pm$  SEM for all of the variables. GraphPad Prism software version 8.0 for Windows (Graphpad Software, San Diego, CA, USA). The data distribution was assessed using the Shapiro-Wilk Test and found to be parametric. Data were then analyzed using ANOVA, followed by Tukey's Post hoc test. Statistical significance was set at  $P < 0.05$ .

## Results

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## Discussion

The present study investigated the impact of monosodium glutamate (MSG), L-arginine, and their co-administration on oxidative stress markers, calcium homeostasis, redox balance, growth factor signaling, and antioxidant defense mechanisms in plasma and cardiac tissues. These findings were corroborated in Figs. 1–4, which showed that MSG significantly reduced SERCA2a, plasma and cardiac calcium levels, NADPH, G6PDH, NO, PI3K, and plasma VEGF compared with the control group. Also, MSG showed a significant increase in cardiac MDA. L-ARG showed a significant increase in SERCA2a, plasma and cardiac calcium levels, NADPH, G6PDH, GPx, NO, VEGF, and PI3K when compared with the control and MSG groups (Figs. 1–4). Co-administration of MSG and L-ARG significantly increased SERCA2a, plasma G6PDH, and GPx (Figs. 1a, 2b & 2c), as well as cardiac NADPH and GPx (Figs. 2d & 2f), while significantly reducing cardiac G6PDH and plasma MDA (Figs. 2e & 3c) compared with the MSG groups. It showed that MSG reduced VEGF expression, PI3K activity, and disrupted calcium regulation, evidenced by reduced  $\text{Ca}^{2+}$ , nitric oxide (NO), NADPH, G6PDH, suppressed SERCA2a expression, and elevated malondialdehyde (MDA). L-arginine improved these parameters, supporting its role in restoring antioxidant capacity and calcium signaling.

MSG exposure resulted in a marked reduction in calcium levels in both plasma and cardiac tissue, with a more pronounced effect in the heart, and was associated with decreased expression of cardiac SERCA2a, a key  $\text{Ca}^{2+}$  ATPase involved in calcium reuptake and contractility [12]. These findings align with earlier reports showing that MSG impairs calcium cycling and promotes dysfunction through glutamate toxicity and oxidative stress [7,24]. The greater reduction in cardiac calcium highlights the heart's vulnerability, given its dependence on excitation-contraction coupling [9]. Previous research highlights the fundamental role of SERCA2a in modulating cardiac contractility, with its activity being crucial for sarcoplasmic reticulum calcium uptake and overall myocardial function. Overexpression of SERCA2a, for example, has been shown to improve cardiac function. This is by increasing coronary blood flow and enhancing nitric oxide production through increased eNOS levels and phosphorylation.

Nitric oxide (NO), a regulator of endothelial function and SERCA2a activity, was markedly reduced by MSG. Since NO enhances SERCA2a

via S-nitrosylation and supports vasodilation, its depletion likely contributed to cardiac impairment, as indicated by previous research [17,14]. Our study reveals that L-arginine restored nitric oxide levels (Figs. 3a & 3b), which, as a physiological precursor, enhanced SERCA2a function through S-nitrosylation. Hence, it facilitates  $\text{Ca}^{2+}$  reuptake and supports myocardial relaxation. This action preserves SERCA2a from oxidative impairment, stabilizes calcium cycling, reduces cardiomyocyte injury, and ultimately improves myocardial function as seen in the current study. This is through reduction in ROS accumulation, diminished lipid peroxidation, and restored redox balance, consistent with earlier work by Oyabambi et al. [25,26]. The present findings advance this trajectory by identifying SERCA2a regulation as an additional mechanism of protection. These effects were notably more pronounced in cardiac tissue than in plasma, suggesting a tissue-specific cardioprotective role for L-arginine via direct modulation of calcium-regulatory and redox-sensitive pathways. The enhancement of SERCA2a activity by L-arginine is consistent with its established role in improving myocardial energetics and combating adverse cardiac remodeling [27]. Activated PI3K/Akt has shown to inactivate procaspase-9 and inhibit FASL synthesis, a transmembrane protein associated altered cell growth and survival [28] and the enhancement of growth factor (VEGF) and activation of PI3K by L-arginine in this study help to establish the improved cardiac function associated with SERCA2a and reduced apoptosis and free radical generation.

MSG also significantly increased MDA levels in cardiac tissue with no significant effect on those of the plasma (Figs. 3c & 3d), reflecting lipid peroxidation and oxidative damage. This was accompanied by declines in NADPH, G6PDH, and GPx, with greater depletion in cardiac tissue. These enzymes are vital for glutathione recycling and redox balance; their depletion under MSG stress reflects overwhelmed antioxidant defenses, consistent with cardiac vulnerability due to high mitochondrial activity and ROS generation [4,10,11]. Thus, myocardial antioxidant defenses become compromised, leading to oxidative injury that impairs membrane integrity and calcium handling. Redox homeostasis was further disrupted by suppression of NADPH and G6PDH, key components of the pentose phosphate pathway. As NADPH fuels glutathione recycling, its depletion impairs antioxidant capacity. L-arginine treatment restored cardiac NADPH following MSG exposure, although plasma improvements were minimal, suggesting a preferential

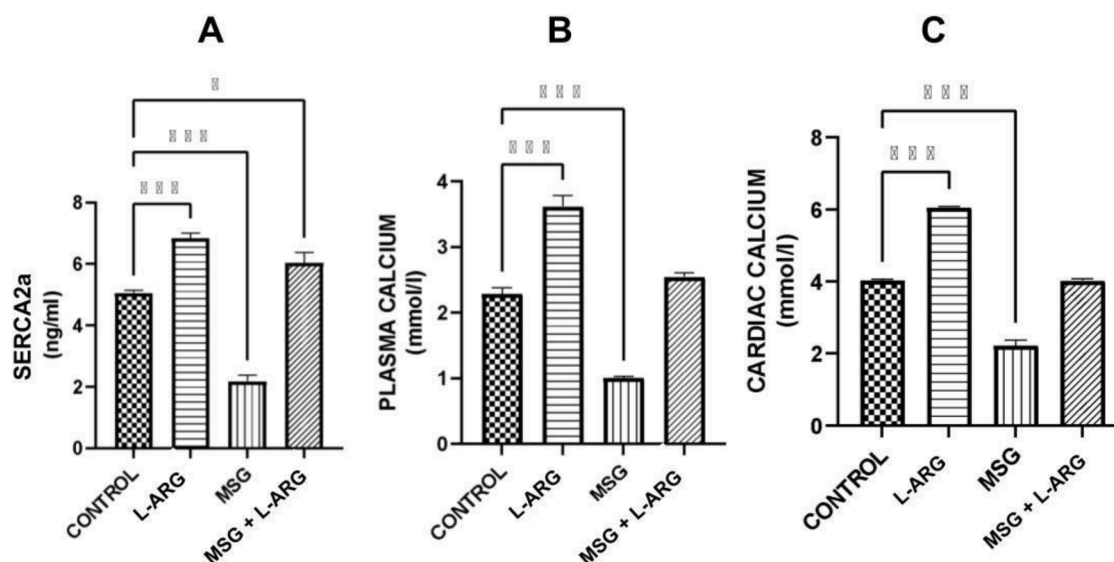


**Fig. 1.** Effects of L-ARG on SERCA2a, plasma, and cardiac calcium in MSG induced cardiotoxicity in male Wistar rats. MSG significantly reduced SERCA2a expression, as well as plasma and cardiac calcium levels ( $***p < 0.001$  vs. Control). In contrast, L-ARG significantly increased SERCA2a (a), plasma calcium (b), and cardiac calcium (c) levels ( $***p < 0.001$  vs. Control). Co-administration of MSG and L-ARG significantly increased SERCA2a levels compared to both MSG and the Control groups ( $*p < 0.05$ ), while it was insignificant in the plasma and cardiac tissue. Data were analyzed by one-way ANOVA followed by Tukey's post hoc test. Values are expressed as mean  $\pm$  SEM of 5 rats per group, and  $p < 0.001$  and  $p < 0.05$  were taken as statistically significant.

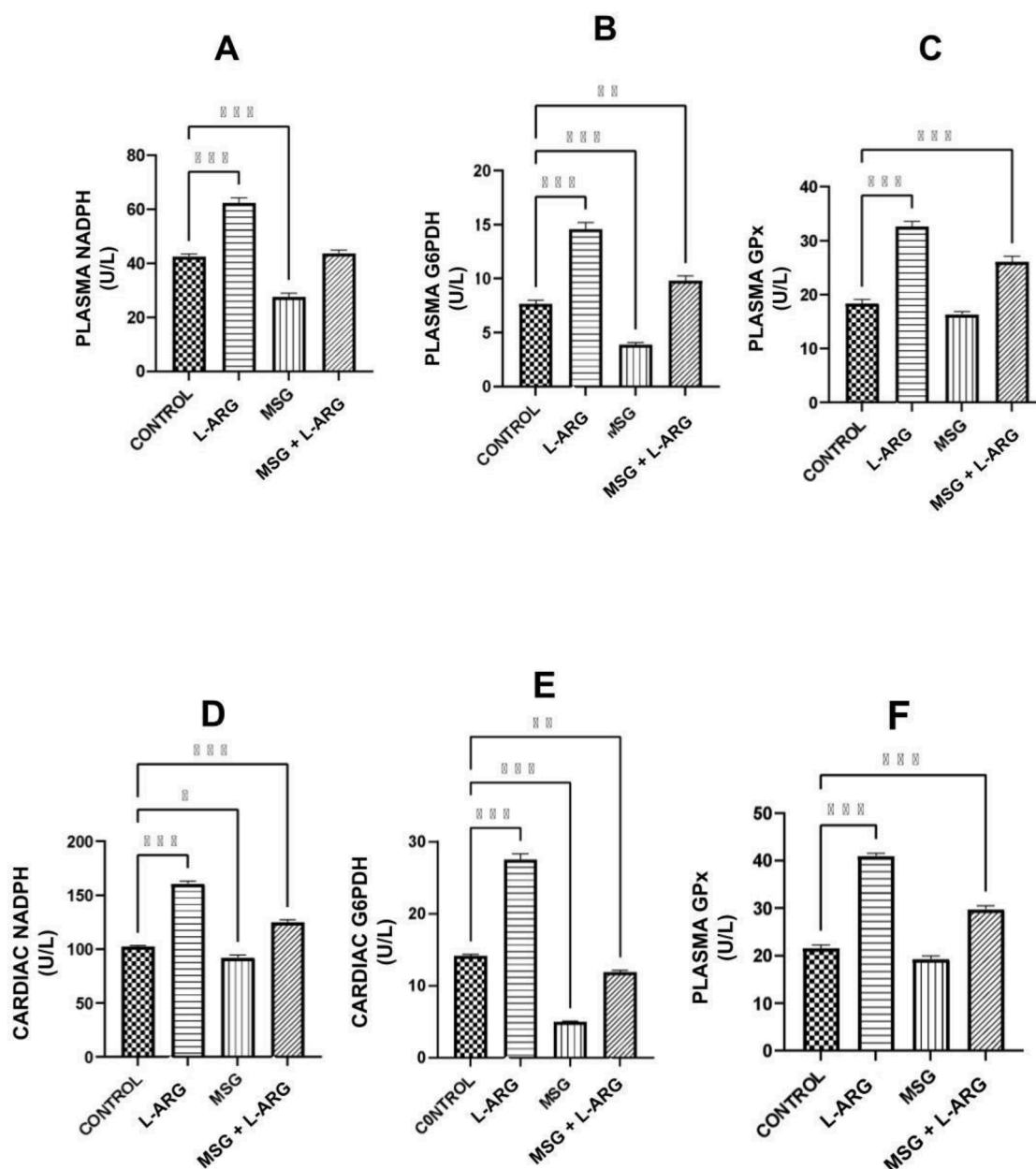


**Fig. 2.** Effects of L-ARG on plasma and cardiac antioxidant parameters [Glucose-6-Phosphate Dehydrogenase (G6PDH), Nicotinamide adenine dinucleotide phosphate (NADPH) & Glutathione peroxidase (GPx)] in MSG induced cardiotoxicity in Male Wistar rats. MSG significantly reduced plasma levels of NADPH and G6PDH ( $***p < 0.001$  vs. Control), but had no significant effect on plasma GPx. In contrast, L-ARG significantly increased plasma NADPH, G6PDH, and GPx levels ( $***p < 0.001$  vs. Control). In cardiac tissue, MSG led to a significant reduction in NADPH ( $*p < 0.05$  vs. Control) and G6PDH ( $***p < 0.001$  vs. Control), while GPx levels remained insignificant. Conversely, L-ARG significantly increased cardiac NADPH, G6PDH, and GPx levels ( $***p < 0.001$  vs. Control). Co-administration of MSG and L-ARG significantly increased plasma G6PDH ( $**p < 0.01$ ), plasma GPx ( $***p < 0.001$ ), as well as cardiac NADPH ( $***p < 0.001$ ) and GPx ( $***p < 0.001$ ) compared to the Control, while plasma statistically insignificant in the plasma. However, cardiac G6PDH showed a significant decrease in comparison with the control group following the co-administration ( $**p < 0.01$ ). Data were analyzed by one-way ANOVA followed by Tukey's post hoc test. Values are expressed as mean  $\pm$  SEM of 5 rats per group, and  $p < 0.001$ ,  $p < 0.01$ , and  $p < 0.05$  were taken as statistically significant.

myocardial demand for NADPH during oxidative stress.

Glutathione peroxidase (GPx), which detoxifies hydrogen peroxide using NADPH-derived reducing equivalents, was also diminished after MSG exposure, allowing ROS accumulation and lipid peroxidation. L-arginine restored GPx activity in both cardiac and plasma tissues (Figs. 2c & 2f), likely through enhanced NADPH availability in the cardiac tissues and NO-mediated signaling [29,16]. These biochemical findings further explain the oxidative and metabolic disturbances underlying MSG-induced cardiotoxicity in relation to SERCA2a dysregulation.

Beyond calcium handling and oxidative stress, MSG also significantly

decreased VEGF expression and PI3K activity which are crucial for cell survival and growth. This is further supported by studies showing that oxidative stress impairs Akt activation [19], while interventions that enhance PI3K/Akt improve the Bcl-2/Bax ratio and reduce apoptosis [30]. The observed increases in malondialdehyde and depletion of NADPH, G6PDH, and glutathione peroxidase following MSG exposure elucidate more on the profound oxidative stress and compromised antioxidant defenses in relation to PI3K. L-ARG group showed a significant increase in this context, indicating that its protective effects extend to include VEGF-PI3K/Akt survival signaling. L-arginine restored both plasma and cardiac GPx and G6PDH activities, as well as cardiac NADPH

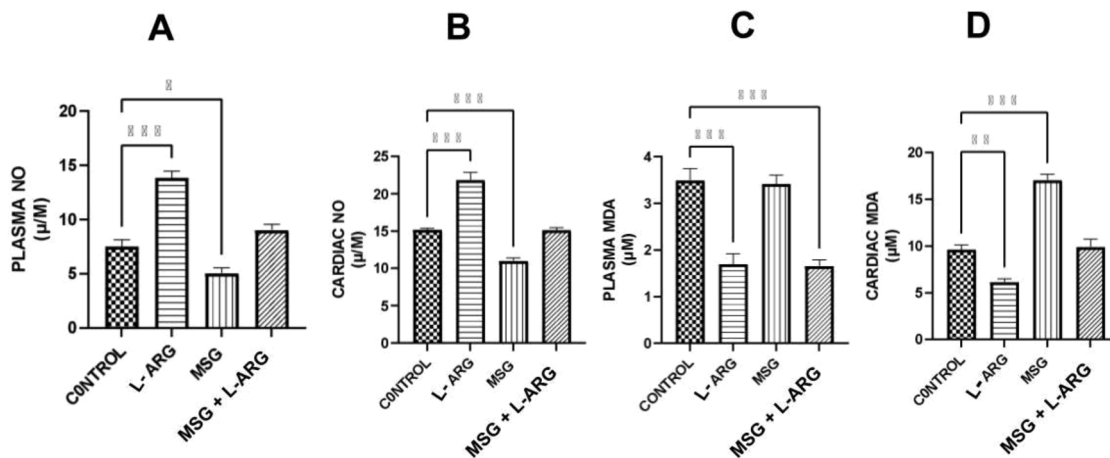


**Fig. 3.** Effects of L-ARG on plasma and cardiac oxidative stress markers [Nitric oxide (NO) and Malondialdehyde (MDA)] in MSG induced cardiotoxicity in male Wistar rats. MSG significantly decreased plasma ( $*p < 0.05$ ) and cardiac ( $***p < 0.001$ ) nitric oxide (NO) levels compared to the Control, while it significantly increased cardiac malondialdehyde (MDA) levels ( $***p < 0.001$ ) with no significant effect on plasma MDA. Conversely, L-ARG significantly increased both plasma and cardiac NO levels ( $***p < 0.001$ ) and reduced plasma ( $***p < 0.001$ ) and cardiac ( $**p < 0.01$ ) MDA levels considerably. Co-administration of MSG and ARG significantly reduced plasma MDA compared to the Control, but showed no statistically significant changes in the other parameters. Data were analyzed by one-way ANOVA followed by Tukey's post hoc test. Values are expressed as the mean  $\pm$  SEM of 5 rats per group.  $p < 0.001$ ,  $p < 0.01$ , and  $p < 0.05$  were considered statistically significant.

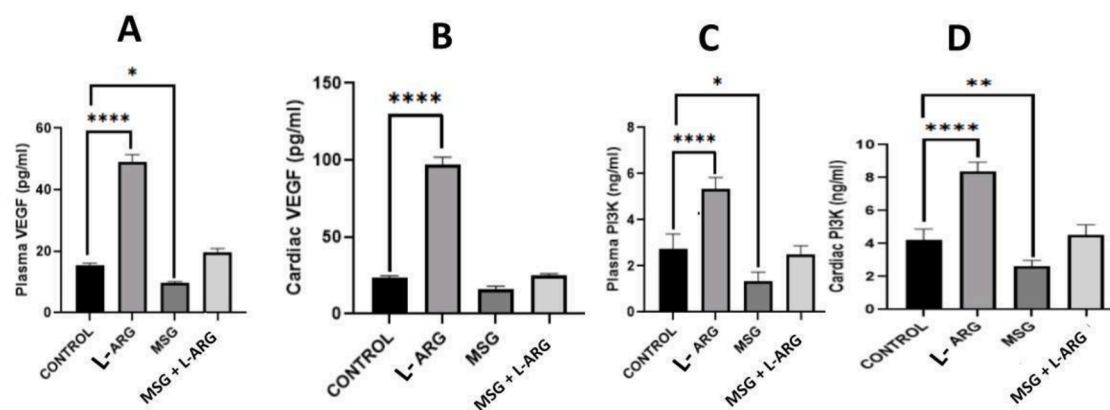


**Fig. 4.** Effects of L-ARG on plasma and cardiac Vascular Endothelial Growth Factor (VEGF) and Phosphoinositide 3-kinase (PI3K) in MSG-induced cardiotoxicity in male Wistar rats. L-ARG significantly increased both plasma ( $****p < 0.0001$ ) and cardiac ( $****p < 0.0001$ ) VEGF levels compared to the Control, while MSG alone showed a decrease in VEGF in plasma ( $*p < 0.0001$ ) with no significant effect in the cardiac tissue. Relative to MSG, co-administration of L-ARG and MSG showed no significant difference in both plasma and cardiac tissues, although values remained higher than those of the Control. For PI3K, L-ARG increased plasma ( $****p < 0.0001$ ) and cardiac ( $****p < 0.0001$ ) levels compared to the Control, while MSG alone markedly decreased both plasma ( $**p < 0.01$ ) and cardiac ( $**p < 0.001$ ) PI3K levels. Combined L-ARG and MSG treatment showed no significant difference in plasma and cardiac PI3K levels relative to MSG and control. Data were analyzed by one-way ANOVA followed by Tukey's post hoc test. Values are expressed as mean  $\pm$  SEM of 5 rats per group, and  $p < 0.05$ ,  $p < 0.01$ , and  $p < 0.001$  were taken as statistically significant.

level (Figs. 2b-2f). Thus, it sustains antioxidant defenses via the pentose phosphate pathway and NO-mediated signaling. This restoration of redox balance aligns with earlier work by Oyabambi et al. and supports the notion that L-arginine mitigates lipid and glucose accumulation through enhancement of PI3K activities [22]. However, there was no significant difference following the co-administration of MSG and L-ARG.

Our findings, informed by the study's results and previous research, demonstrate that L-arginine significantly contributes to improved cardiac function and overall cardiac health by increasing both SERCA2a activity and PI3K/VEGF signaling attenuated by monosodium glutamate. Monosodium glutamate induces cardiotoxicity by disrupting calcium homeostasis [31]. This may have potentiated the reduced SERCA2a expression and activity, which are crucial for myocardial relaxation and excitation-contraction coupling. L-arginine, as a precursor for nitric oxide, restores NO levels, which in turn enhance SERCA2a

function through S-nitrosylation [32,33]. This mechanism facilitates efficient  $\text{Ca}^{2+}$  reuptake and stabilizes calcium cycling. It also promotes myocardial relaxation, thereby directly improving contractile function and preventing calcium overload and cardiomyocyte injury [33]. Concurrently, MSG in this study impairs VEGF expression and PI3K activity and L-arginine increased it (Fig. 4). This restoration supports L-arginine's ability to increase neovascularization and combats oxidative stress, as oxidative stress can impair Akt activation.

## Conclusion

In summary, L-arginine preserved SERCA2a from oxidative impairment, stabilized calcium cycling, reduced cardiomyocyte injury, and improved myocardial function. Its effects were more pronounced in cardiac tissue than plasma, highlighting a tissue-specific cardioprotective role via direct modulation of calcium-regulatory and

redox-sensitive pathways. Therefore, L-arginine's multi-faceted action optimizes SERCA2a activity for enhanced cardiac performance and restores VEGF-PI3K/Akt signaling for improved cell survival and angiogenesis. Through this, it comprehensively protects against MSG-induced cardiotoxicity and contributes to the overall health and resilience of the heart.

### Limitations

While our biochemical findings provide compelling evidence for L-arginine's cardioprotective effects, some limitations warrant discussion. One specific observation noted was that combined MSG + L-arginine treatment sometimes resulted in certain levels (e.g. plasma and cardiac VEGF levels) exceeding those of the control group. This complex response could be attributed to several factors. Research indicates that uncontrolled production of NO in an oxidative environment can lead to the formation of peroxynitrite (ONOO<sup>-</sup>), a highly damaging reactive nitrogen species [15]. Such paradoxical effects of L-arginine have been documented; for instance, L-arginine supplementation during the late stage of reperfusion has been shown to increase infarct size and peroxynitrite formation in rats [15]. This suggests a delicate balance where excessive NO production, especially in the presence of oxidative stress, might shift from beneficial to detrimental, leading to an amplified or overcompensated biological response. Moreover, L-arginine supplementation stimulates NO production even when plasma L-arginine levels are within physiological limits, often involving interactions with L-glutamine or competition for enzyme binding [16].

Furthermore, as noted within our source, while the biochemical evidence is robust, additional validation through techniques such as histology or echocardiography would provide a more comprehensive understanding of the structural and functional improvements. Future research could incorporate such multidimensional approaches to further reinforce the critical role of SERCA2a in cardioprotection.

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### Data availability

Data will be made available on request from the corresponding author.

### Consent to participate, and consent to publish declaration

I/We, the undersigned authors, declare that we have all made significant contributions that fulfil the Next Research Journal authorship recommendation to this manuscript and agree to its submission to Next Research Journal and, if accepted, to its publication in this journal. Ethical approval has been sought and obtained as necessary, and any conflicts of interest are stated in the manuscript.

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This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors. The article also gets no external funding from any organization or from where I work. The article is a pet contribution from the authors to the field of science and global knowledge. Also, the work is done in Nigeria, a low- and middle-income earning country. I therefore request a waiver for the publication of the article.

### CRediT authorship contribution statement

**Adewumi Oluwafemi Oyabambi:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bosede Christianah Oyakojo:** Methodology, Formal analysis, Data curation, Conceptualization. **Emmanuel Eytayo Oguntebi:** Validation, Supervision, Methodology, Formal analysis. **Atinuke Alice Oyabambi:** Writing – original draft, Methodology, Investigation, Data curation. **Olanrewaju Amos Ajayi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### References

- [1] P. Joseph, D. Leong, M. McKee, S.S. Anand, J.-D. Schwalm, K. Teo, A. Mente, S. Yusuf, Reducing the global burden of cardiovascular disease, part 1: the epidemiology and risk factors, *Circ. Res.* 121 (6) (2017) 677–694.
- [2] O. Erbaş, I. Altuntaş, Ö. Çağlar, E. Özyılmaz, E. Sarı, İ. Üzümcü, K. Erbakan, Experimental model of cardiotoxicity, *Risk Factors Cardiovasc. Dis.* (2022) 187.
- [3] S. Yusuf, P. Joseph, S. Rangarajan, S. Islam, A. Mente, P. Hystad, M. Brauer, V. R. Kutty, R. Gupta, A. Wielgosz, Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study, *Lancet* 395 (10226) (2020) 795–808.
- [4] A. Banerjee, S. Mukherjee, B.K. Maji, Worldwide flavor enhancer monosodium glutamate combined with high lipid diet provokes metabolic alterations and systemic anomalies: an overview, *Toxicol. Rep.* 8 (2021) 938–961.
- [5] K. Kahe, B. Laferrière, F.X. Castellanos, Y. Zhang, D. Mozaffarian, Monosodium glutamate: a hidden risk factor for obesity? *Obes. Rev.* 26 (6) (2025) e13903.
- [6] S. Shrestha, C. Jha, B. Das, P. Yadav, Effects of monosodium glutamate on liver tissue of Wistar albino rats—a histological and biochemical study, *Exp. Anim.* 8 (10) (2018).
- [7] S.M. Hazzaa, E.S. El-Roghy, M.A. Abd Eldaim, G.E. Elgarawany, Monosodium glutamate induces cardiac toxicity via oxidative stress, fibrosis, and P53 proapoptotic protein expression in rats, *Env. Sci. Pollut. Res.* 27 (2020) 20014–20024.
- [8] S.P. Konrad, V. Farah, B. Rodrigues, R.B. Wichi, U.F. Machado, H.F. Lopes, B.D. A. Schaan, K.D. Angelis, M.C. Irigoyen, Monosodium glutamate neonatal treatment induces cardiovascular autonomic function changes in rodents, *Clinics* 67 (2012) 1209–1214.
- [9] D.A. Eisner, J.L. Caldwell, K. Kistamás, A.W. Trafford, Calcium and excitation-contraction coupling in the heart, *Circ. Res.* 121 (2) (2017) 181–195.
- [10] N. Panday, D. Sigdel, I. Adam, J. Ramirez, A. Verma, A.N. Eranki, W. Wang, D. Wang, P. Ping, Data-driven insights into the association between oxidative stress and calcium-regulating proteins in cardiovascular disease, *Antioxidants* 13 (11) (2024) 1420.
- [11] S. Singh, U. Mabalirajan, Mitochondrial calcium in command of juggling myriads of cellular functions, *Mitochondrion* 57 (2021) 108–118.
- [12] J. Frago-Medina, A. Zarain-Herzberg, SERCA2a: its role in the development of heart failure and as a potential therapeutic target, *Res. Rep. Clin. Cardiol.* (2014) 43–55.

- [13] L. Zhihao, N. Jingyu, L. Lan, S. Michael, G. Rui, B. Xiyun, L. Xiaozhi, F. Guanwei, SERCA2a: a key protein in the Ca<sup>2+</sup> cycle of the heart failure, *Heart. Fail. Rev.* 25 (2020) 523–535.
- [14] D. Cylwik, A. Mogielnicki, W.o. Buczko, L-arginine and cardiovascular system, *Pharmacol. Rep.* 57 (1) (2005) 14–22.
- [15] E. Sudar-Milovanovic, M. Obradovic, A. Jovanovic, B. Zaric, S. Zafirovic, A. Panic, D. Radak, E. R Isenovic, Benefits of L-arginine on cardiovascular system, *Mini. Rev. Med. Chem.* 16 (2) (2016) 94–103.
- [16] G. Wu, C.J. Meininger, C.J. McNeal, F.W. Bazer, J.M. Rhoads, Role of L-arginine in nitric oxide synthesis and health in humans. *Amino Acids in Nutrition and Health*, Springer, 2021, pp. 167–187.
- [17] P.K. Chohan, R.B. Singh, N.S. Dhalla, T. Netticadan, L-arginine administration recovers sarcoplasmic reticulum function in ischemic reperfused hearts by preventing calpain activation, *Cardiovasc. Res.* 69 (1) (2006) 152–163.
- [18] A.M. Evangelista, M.D. Thompson, R.M. Weisbrod, D.R. Pimental, X. Tong, V. M. Bolotina, R.A. Cohen, Redox regulation of SERCA2 is required for vascular endothelial growth factor-induced signaling and endothelial cell migration, *Antioxid. Redox. Signal.* 17 (8) (2012) 1099–1108.
- [19] Z.Y. Zhang, L. Pan, S. Dang, R.X. Wang, et al., Glucose fluctuations aggravate cardiomyocyte apoptosis by up-regulating txnip expression and enhancing Txnip–Akt interaction, *BMC. Cardiovasc. Disord.* 24 (2024) 470.
- [20] P.H. Andrews, B.B. Carter, D.P. Shah, E.A. Roberts, M.E. Thompson, Clinical associations and potential cellular mechanisms linking G6PD deficiency and atherosclerotic cardiovascular disease, *npj Metab. Health Dis.* 3 (1) (2025) 16.
- [21] F.F. Jubaidi, R.D. Mathialagan, M.M. Noor, I.S. Taib, S.B. Budin, Monosodium glutamate daily oral supplementation: study of its effects on male reproductive system on rat model, *Syst. Biol. Reprod. Med.* 65 (3) (2019) 194–204.
- [22] A.O. Oyabambi, O. Bamidele, B.B. Aindero, A.M. Awolola, L-arginine mitigates cardiac lipid and glucose accumulation through leptin modulation and enhancement of PI3K activities in high-fat-fed male Wistar rats, *Nutr. Metab.* 21 (1) (2024) 103.
- [23] A.O. Oyabambi, O.S. Michael, E.D. Areola, et al., Sodium acetate ameliorated systemic and renal oxidative stress in high-fructose insulin-resistant pregnant Wistar rats, *Naunyn-Schmiedeb. Arch Pharmacol.* 394 (2021) 1425–1435.
- [24] M.A. Mohamed, W.A. El-Nahrawy, A.M. Zaher, A.S. Amer, Protective and/or therapeutic effects of curcumin nanoparticles on monosodium glutamate induced cardiotoxicity in male Albino rats, *Egypt. Acad. J. Biol. Sci. B. Zool.* 15 (2) (2023) 139–159.
- [25] A.O. Oyabambi, B. Olubayode, B. Aindero, Butyrate ameliorates lithium-induced cardiometabolic disorders in male Wistar rats, *Sci. Afr.* 20 (2023) e01697.
- [26] A.O. Oyabambi, S.O. Kehinde, O.S. Ayodele, A.O. Lawrence, Suppression of uric acid and lactate production by sodium acetate ameliorates hepatic triglyceride accumulation in fructose-insulin resistant pregnant rats, *Env. Toxicol. Pharmacol.* 80 (2020) 103452.
- [27] A. Fiordelisi, F.A. Cerasuolo, R. Avvisato, A. Buonaiuto, M. Maisto, A. Bianco, V. D'Argenio, P. Mone, C. Perrino, S. D'Apice, L-arginine supplementation as mitochondrial therapy in diabetic cardiomyopathy, *Cardiovasc. Diabetol.* 23 (1) (2024) 450.
- [28] V. Bhatia, V. Vikram, A. Chandel, et al., Interplay between PI3k/AKT signaling and caspase pathway in Alzheimer disease: mechanism and therapeutic implications, *Inflammopharmacol* 33 (2025) 1785–1802.
- [29] D.L. Saifaddin, S.S. Mohammed, H.A. Rahim, N. Ghanbari, D.A. Kareem, H. H. Abdollah, S.M. Omar, Endurance training and L-arginine intake: their effect on antioxidant indices in the heart muscles of rats, *Nutr. Health* 31 (2) (2025) 471–476.
- [30] F. Zhao, Q. Liu, J. Cao, Y. Xu, Z. Pei, H. Fan, Y. Yuan, X. Shen, C. Li, A sea cucumber (*Holothuria leucospilota*) polysaccharide improves the gut microbiome to alleviate the symptoms of type 2 diabetes mellitus in Goto-Kakizaki rats, *Food Chem. Toxicol.* 135 (2020) 110886.
- [31] O.-L. Moldovan, C.-E. Vari, A. Tero-Vescan, O.S. Cotoi, I.G. Cocuz, F.A. Tabaran, R. Pop, I. Fülöp, R.F. Chis, I.-A. Lungu, Potential defence mechanisms triggered by monosodium glutamate sub-chronic consumption in two-year-old Wistar rats, *Nutrients.* 15 (20) (2023) 4436.
- [32] S.M. Andrabi, N.S. Sharma, A. Karan, S.S. Shahriar, B. Cordon, B. Ma, J. Xie, Nitric oxide: physiological functions, delivery, and biomedical applications, *Adv. Sci.* 10 (30) (2023) 2303259.
- [33] G. Kayki-Mutlu, W.J. Koch, Nitric oxide and S-nitrosylation in cardiac regulation: g protein-coupled receptor kinase-2 and  $\beta$ -arrestins as targets, *Int. J. Mol. Sci.* 22 (2) (2021) 521.