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# Protective Antioxidant Role of *Citrullus lanatus* Rind Extract Against Monosodium Glutamate-Induced Oxidative Stress in Cardiac Tissue of Albino Rats

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**ABSTRACT**

***Background*:** Excessive intake of monosodium glutamate (MSG) has been implicated in the induction of oxidative stress, leading to structural and functional impairment in various tissues, including the heart. Increasing attention has been directed toward naturally derived antioxidants as safer and sustainable therapeutic alternatives.

***Methods*:** Thirty-six male albino rats were randomly allocated into six experimental groups (n = 6). Oxidative stress was induced via oral administration of MSG (8000 mg/kg body weight). Treatment groups received graded doses of *Citrullus lanatus* rind extract (200, 400, and 600 mg/kg body weight) alongside a standard antioxidant (vitamin C) for 28 days. Cardiac tissue homogenates were analyzed for antioxidant indices including superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), glutathione peroxidase (GPx), malondialdehyde (MDA), and vitamins C and E using established biochemical protocols.

***Results:*** MSG exposure significantly elevated MDA levels while suppressing endogenous antioxidant enzymes ($p < 0.05$). Administration of *Citrullus lanatus* rind extract resulted in a marked reversal of these alterations, evidenced by decreased lipid peroxidation and restoration of antioxidant enzyme activities.

***Conclusion*:** The rind extract of *Citrullus lanatus* demonstrates potent cardioprotective antioxidant properties and may represent a viable natural alternative in mitigating MSG-induced oxidative cardiac damage.

***Keywords*:** Cardiac antioxidants, Citrullus lanatus, lipid peroxidation, MSG toxicity, Oxidative stress.

## 1. INTRODUCTION

Oxidative stress is characterized by an imbalance between pro-oxidant generation and antioxidant defense capacity, ultimately leading to cellular dysfunction and tissue injury [1-5]. Reactive oxygen species (ROS), when produced excessively, can damage biomolecules including lipids, proteins, and nucleic acids, contributing to the pathogenesis of numerous diseases [3-5]. Monosodium glutamate (MSG), a widely utilized flavor enhancer, has been reported to induce oxidative stress when consumed in high quantities. Previous investigations have demonstrated that MSG exposure promotes lipid peroxidation and reduces antioxidant enzyme activity in several organs [6-8,39]. The myocardium is particularly vulnerable due to its high metabolic demand and continuous oxygen utilization [9]. Natural antioxidants have gained increasing scientific interest due to their safety profile and multifaceted mechanisms of action. *Citrullus lanatus*, though primarily consumed for its pulp, possesses a rind that is rich in phytochemicals such as flavonoids, phenolic compounds, and citrulline [10-12,37]. These bioactive constituents are known to exhibit free radical scavenging activity and enhance endogenous antioxidant systems [13-15,29]. Although several studies have explored plant-derived antioxidants, limited research has focused specifically on the cardioprotective effects of watermelon rind under chemically induced oxidative stress conditions. Therefore, this study was designed to evaluate the antioxidant efficacy of *Citrullus lanatus* rind extract in mitigating MSG-induced oxidative damage in rat heart tissue.

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## 2. MATERIALS AND METHODS

### 2.1 Materials

*2.1.1 Biological Materials*

Male albino rats (*Rattus norvegicus*)

*2.1.2 Chemicals and Reagents*

Monosodium glutamate (MSG), Thiobarbituric acid, Distilled water, Assay kits for the determination of superoxide dismutase (SOD), Catalase (CAT), Vitamin C, Vitamin E, Malondialdehyde (MDA), glutathione peroxidase (GPx) and reduced glutathione (GSH) in the rats' heart homogenates were purchased from Randox, UK. All other chemicals were of analytical grade.

*2.1.3 Equipment*

Colorimeter (A CO75 digital colorimeter. Binton Cambridge, UK.), Refrigerator (Superpower refrigerator. Made by Philco-company Ltd. UK/China), Water Bath (Betra BL-410S, Liquitherm F. Manufacturer. Clinician International GMBH, England), Centrifuge (Hettich universal centrifuge England (Universal 320 series). manufactured by Andreas Hettich, Tuttlingen, Germany), Spectrophotometer (Uniscope 23D spectrophotometer (England). All analyses followed standard instrumental procedures [42–44].

### 2.2 Methods

*2.2.1 Preparation of Extract*

*Citrullus lanatus* rinds were thoroughly washed, air-dried, and blended. The homogenate was macerated in distilled water for 8 hours at ambient temperature and subsequently filtered using muslin cloth to obtain the aqueous extract.

*2.2.2 Acute Toxicity ($LD_{50}$)*

Toxicological evaluation was conducted using Lorke's method [16]. No mortality was observed at doses up to 5000 mg/kg body weight, indicating relative safety of the extract.

*2.2.3 Experimental Design*

Thirty-six rats were divided into six groups:

- Group A: Normal control
- Group B: MSG (8000 mg/kg)
- Group C: Extract only (400 mg/kg)
- Group D: MSG + extract (200 mg/kg)
- Group E: MSG + extract (400 mg/kg)
- Group F: MSG + extract (600 mg/kg)

All treatments were administered orally for 28 days. The MSG dose was selected based on established models of oxidative stress induction [6–8].

*2.2.4 Tissue Collection*

Animals were euthanized under appropriate anesthesia. Heart tissues were excised, rinsed in saline, homogenized, and prepared for biochemical assays.

*2.2.5 Biochemical Assays*

*2.2.5.1 Preparation of Heart Homogenates*

Heart tissues were collected from each rat immediately after blood collection and rinsed in 0.01 M phosphate buffer to remove blood residues. A weighed portion (0.5 g) of the tissue was homogenized using a mortar and pestle and diluted with 0.01 M phosphate buffer in a ratio of 1:9 (w/v; tissue weight to buffer volume). The homogenate was centrifuged at 3,000 rpm for 5 minutes, and the resulting supernatant was carefully collected for biochemical analysis. All samples and reagents were equilibrated to room temperature prior to analysis. The stock wash buffer was diluted with deionized water to prepare 750 mL of working buffer solution as required.

*2.2.6. Determination of Enzymatic Antioxidants*

*2.2.6.1 Determination of superoxide dismutase (SOD) activity*

Superoxide dismutase (SOD) is an oxidoreductase enzyme that catalyzes the dismutation of superoxide radicals ($O_2^-$) into molecular oxygen ($O_2$) and hydrogen peroxide ($H_2O_2$) [17,45,46]. SOD activity was determined according to the method of McCord and Fridovich [17]. In this assay, superoxide radicals are generated and their presence is monitored through the oxidation of adrenaline to adrenochrome, which produces a measurable increase

in absorbance. SOD activity is evaluated based on its ability to inhibit this reaction. One unit of SOD activity is defined as the amount of enzyme required to produce 50% inhibition of the reaction under the assay conditions. Briefly; Adrenaline solution was prepared by dissolving 0.01 g of adrenaline in 17 mL of distilled water. A mixture of 0.1 mL of sample and 0.9 mL of phosphate buffer was prepared. From this, 0.2 mL was taken in triplicate and added to 2.5 mL of phosphate buffer. In the cuvette, 3.0 mL of adrenaline solution was added, and the absorbance was measured at 480 nm at 30-second intervals for 5 readings. A control without sample was run simultaneously. Results were expressed as U/mL. percentage inhibition was calculated as follows:

$$\% \text{ Inhibition} = \frac{(A_0 - A_s)}{A_0} \times 100$$

Where: $A_0$= absorbance of the control; $A_s$= absorbance of the sample

*2.2.6.2 Determination of catalase (CAT) activity.*

Catalase activity was determined using the method of Aebi [18]. Dichromate in acetic acid was reduced to chromic acetates, when heated in the presence of hydrogen peroxide with the formation of perchromic acid as unstable intermediate. The chromic acetate formed was measured at 570 nm. Catalase was allowed to split $H_2O_2$ for different periods of time. The reaction was stopped at different time intervals by the addition of dichromate acetic acid mixture in 1:3 and the remaining $H_2O_2$ was determined by measuring chromic acetate colorimetrically. Riefly**,** to 0.9 mL of distilled water and 0.1 mL of plasma in a test tube was added 2.0 mL of $H_2O_2$ and 2.0 mL phosphate buffer. The reaction was initiated by adding 2.0 mL of dichromate acetic acid reagent to 1.0 mL portion to this mixture. Absorbance of the reaction was taken at 30 s intervals for 2 min. The activity of catalase was expressed as U/mL of plasma (µmol of $H_2O_2$ utilized per second). Catalase activity was calculated using the following equation:

$$\text{Catalytic concentration (U/L)} = 0.23 \times (\log \text{Abs}_1 / \text{Abs}_2) / 0.00693$$

*2.2.6.3 Determination of glutathione peroxidase (GPx) activity.*

Glutathione peroxidase (GPx) activity was determined according to the method of Paglia and Valentine [21]. GPx catalyzes the oxidation of reduced glutathione (GSH) by organic peroxides such as cumene hydroperoxide. In the presence of glutathione reductase (GR) and reduced nicotinamide adenine dinucleotide phosphate (NADPH), the oxidized glutathione (GSSG) is rapidly converted back to GSH, with a simultaneous oxidation of NADPH to $NADP^+$. This reaction leads to a decrease in absorbance at 340 nm, which is directly proportional to GPx activity. The reactions involved are as follows:

$$2GSH + ROOH \rightarrow GSSG + ROH + H_2O$$
$$GSSG + NADPH + H^+ \rightarrow NADP^+ + 2GSH$$

For the assay, 0.05 mL of heparinized whole blood was diluted with 2.0 mL of diluting reagent to prepare the haemolysate. Subsequently, 50 µL of the diluted sample was added to 1.0 mL of reaction mixture containing phosphate buffer with EDTA, glutathione, glutathione reductase, NADPH, and cumene hydroperoxide. The initial absorbance of both the test and blank was recorded at 340 nm after 1 minute, and timing commenced immediately. Absorbance readings were then taken at 1- and 2-minute intervals. Glutathione peroxidase activity was calculated from the rate of decrease in absorbance using the expression:

$$\text{GPx activity (U/L haemolysate)} = 8.12 \times \Delta A_{340}/\text{min}$$

*2.2.6.4 Determination of reduced glutathione (GSH) activity***.**

The assay is based on the reaction of sulphydryl (–SH) groups with 5,5′-dithiobis-(2-nitrobenzoic acid) (DTNB), resulting in the formation of a yellow-colored chromogen measurable at 412 nm using a spectrophotometer.

The reagents used included 0.3 M disodium hydrogen phosphate, 0.1% disodium EDTA, and a precipitating solution composed of 1.67 g metaphosphoric acid, 0.2 g disodium EDTA, and 30 g sodium chloride dissolved in 1 L of distilled water. The DTNB reagent was prepared by dissolving 40 mg of DTNB in 100 mL of 1% sodium citrate solution. A standard solution was prepared using 10 mg of reduced glutathione in 100 mL of distilled water. For the assay, 0.2 mL of the sample was mixed with 1.8 mL of EDTA solution and 3.0 mL of the precipitating reagent, then allowed to stand for 5 minutes before centrifugation. Subsequently, 2.0 mL of the supernatant was transferred and combined with 4.0 mL of 0.3 M disodium hydrogen phosphate and 1.0 mL of DTNB reagent. The

absorbance of the developed yellow color was measured at 412 nm. Standard solutions containing 20–100 mg of reduced glutathione were treated in the same manner, and the results were expressed as mg/dL of plasma [19,20].

*2.2.7 Determination of antioxidant markers*

*2.2.7.1 Malondialdehyde concentration estimation*

Lipid peroxidation was assessed by measuring malondialdehyde (MDA) levels using the thiobarbituric acid reactive substances (TBARS) method [22,47]. The supernatant (50 µL) was deproteinized by adding 1.0 mL of 14% trichloroacetic acid and 1.0 mL of 0.6% thiobarbituric acid. The mixture was heated in a water bath for 30 min to complete the reaction, and then cooled on ice for 5 min. After centrifugation at 2000 × g for 10 min, the absorbance of coloured product (TBARS) was measured at 535 nm with a UV spectrophotometer. Total protein content of the homogenate was determined spectrophotometrically using the Biuret method. The concentration of TBARS was calculated using the molar extinction coefficient of malondialdehyde ($1.56 \times 10^5$ $L \cdot mol^{-1} \cdot cm^{-1}$) using the formula, $A = \varepsilon CL$, where A = absorbance, ε = molar coefficient, C = concentration and L = path length. All TBARS concentration was expressed in µmol/g tissue protein [22]

*2.2.7.2 Determination of vitamin C concentration*

Vitamin C concentration was determined using the method of Emadi-Konji [23, 24, 49, 50].

Briefly, 1.0 mL of the sample was mixed with 1.0 mL of 10% trichloroacetic acid (TCA) and 0.5 mL of chloroform. The mixture was shaken for 15 seconds and centrifuged at 3,000 rpm to obtain a clear supernatant. An aliquot (1.0 mL) of the supernatant was transferred into a clean test tube. Blank and standard solutions were prepared using 0.5 mL of 10% TCA and 0.5 mL of working standard solution. To each tube, 0.4 mL of freshly prepared combined color reagent was added. The tubes were incubated in a water bath at 56°C for 1 hour, then cooled in an ice bath for 5 minutes. Subsequently, 2.0 mL of ice-cold 85% sulphuric acid was added slowly with mixing. The reaction mixtures were allowed to stand at room temperature for 30 minutes, after which absorbance was measured at 490 nm using the blank to zero instrument.

Vitamin C concentration was calculated using the formula:

$$\text{Vitamin C (mg/100 mL)} = \frac{\text{Absorbance of sample} \times \text{Concentration of standard}}{\text{Absorbance of standard}}$$

*2.2.7.3 Determination of vitamin E concentration*

Vitamin E concentration was determined using the method described by Wei [23,24,49,50], with slight modifications. Briefly, 150 mg of anhydrous sodium sulfate ($Na_2SO_4$) was placed in a moisture-free test tube. An aliquot (100 µL) of the sample was added, followed by 2.0 mL of acetone to precipitate proteins. The mixture was vortexed thoroughly, and 500 µL of internal standard solution was added. The mixture was shaken and allowed to stand for 2 hours, then centrifuged for 20 minutes. The supernatant was carefully collected and filtered through a 0.45 µm syringe filter. The residue was rinsed with 1.5 mL of acetone, filtered again, and the combined filtrate was evaporated gently at 40°C to dryness. The dried extract was cooled on ice, reconstituted with 500 µL of chloroform–methanol (1:3, w/v) containing butylated hydroxytoluene (BHT), vortexed, and kept at low temperature (freezer) for 2 hours. An aliquot (50 µL) of the final solution was injected into the HPLC system. Separation was carried out using degassed methanol as the mobile phase at a flow rate of 2.0 mL/min, with detection at 292 nm. The run time was 6 minutes 30 seconds. Quantification was based on a calibration curve of α-tocopherol over the range of 50–500 ng ($r = 0.999$).

**2.3 Statistical Analysis**

Data were expressed as mean ± SD. Statistical significance was evaluated using one-way ANOVA ($p < 0.05$).

**3. RESULT**

MSG administration resulted in a significant elevation in MDA levels, indicating increased lipid peroxidation. Concurrently, there was a marked reduction in antioxidant enzymes (SOD, CAT, GSH, GPx) in comparison with the control group. Vitamins C and E concentrations were also elevated in treated groups, suggesting enhanced non-enzymatic antioxidant defense. Treatment with *Citrullus lanatus* rind extract produced a dose-dependent improvement in antioxidant status. Enzymatic activities were significantly restored, while MDA levels declined, demonstrating reduced oxidative damage. The acute toxicity study revealed no mortality across tested doses, confirming the safety profile of the extract.

### 3.1 Acute Toxicity and Lethality ($Ld_{50}$) Test

Acute systemic toxicity testing is conducted to determine the hazard potential of a single exposure to chemicals or products (by oral, dermal, or respiratory routes). The assessment of lethality, which forms part of acute systemic toxicity testing, relied on the in vivo measurement of the median lethal dose ($LD_{50}$), i.e., the dose of test chemical that kills 50% of the animal in the experimental group. Oral administration of up to 5000 mg/kg body weight of *Citrullus lanatus* rind extract to male albino rats caused no death in the two stages of the test. Thus, oral $LD_{50}$ of the extract in rats was estimated to be greater than 5000 mg/kg body weight, which suggests that the rind paste extract may be generally regarded as safe with a remote risk of acute intoxication. The high degree of safety is also consistent with the report of Omigie et al [41] and its popular use as herbs in the western part of Nigeria.

Table 1: Lethal dose ($LD_{50}$) *Citrullus lanatus* paste extract in male Wister rats

| Phase 1 | Dosage (mg/kg body weight) | Mortality |
|---|---|---|
| Group 1 | 10 | 0/3 |
| Group 2 | 100 | 0/3 |
| Group 3 | 1000 | 0/3 |
| Phase 2 | | |
| Group 1 | 1600 | 0/3 |
| Group 2 | 2900 | 0/3 |
| Group 3 | 5000 | 0/3 |

### 3.2 Effect of *Citrullus lanatus* Rinds Extract on Reduced Glutathione (GSH) activity (U/L).

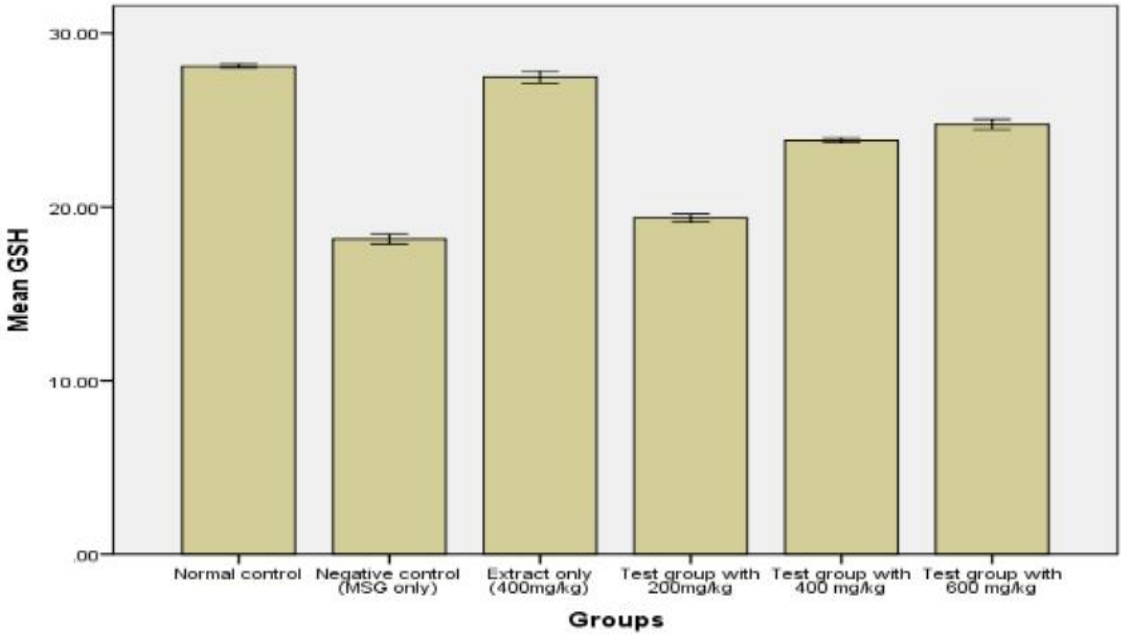


Figure 1: Graph of Reduced Glutathione concentration (Umol/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

Figure 1 shows the effect of different doses of *Citrullus lanatus* rind paste extract on reduced glutathione (GSH) concentration in the experimental rats. There was a significant ($p<0.05$) increase in GSH level in heart homogenate of rats given graded doses of *Citrullus lanatus* rind paste extract in groups E, D, and F (200, 400, and 600 mg/kg body weight respectively) compared with the negative control (group B).

### 3.3 Effect of the *Citrullus lanatus* rind paste extract on Glutathione Peroxidase (GPx) activity (U/L).

GPx activity in heart homogenate of the experimental rats showed significant ($P<0.05$) increase in groups of rats administered oral doses of watermelon rind paste extract at 200, 400 and 600 mg/kg body weight (groups D, E, and F, respectively) compared with the negative control (group B) as presented in Fig 2 below.

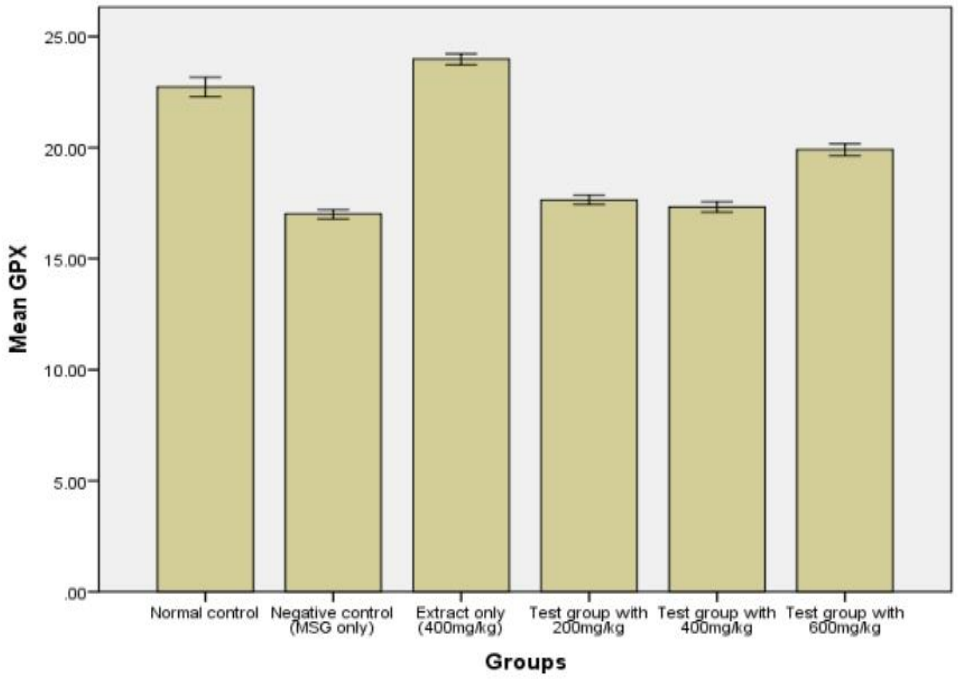


Figure 2: Graph of Glutathione Peroxidase (GPX) activity (U/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

### 3.4. Effect of the *Citrullus lanatus* paste extract on Superoxide dismutase (SOD) activity (U/L).

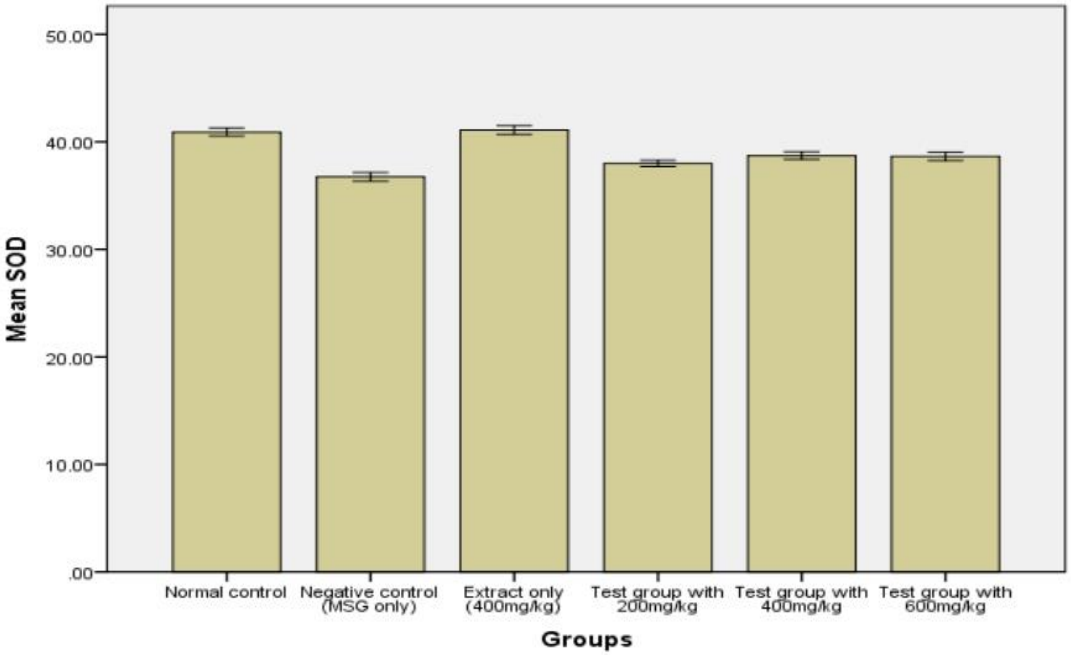


Figure 3: Graph of Superoxide dismutase (SOD) activity (U/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

Figure 3 shows that the oral administration of *Citrullus lanatus* rind extract at the doses of 200, 400, and 600 mg/kg body weight in groups D, E, and F, respectively significantly ($p<0.05$) increased SOD activity in the heart homogenate of the experimental rats as compared to the negative control (group B).

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### 3.5 Effect of the *Citrullus lanatus* rind paste extract on Catalase (CAT) activity (U/L).

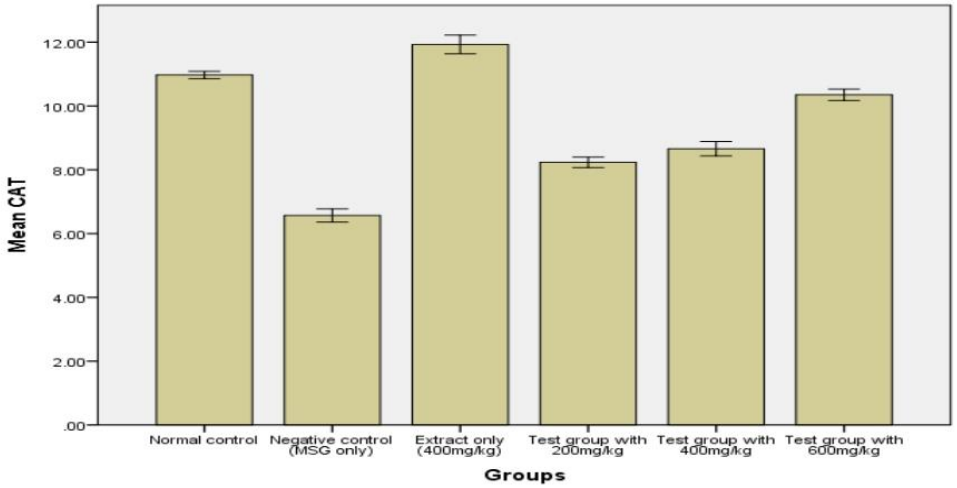


Figure 4: Graph of Catalase (CAT) activity (U/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

In Figure 4, there was significant ($p<0.05$) increase in catalase activity in rats administered oral doses of *Citrullus lanatus* rind extract in groups D, E, and F, (at 200, 400 and 600 mg/kg body weight respectively as against group B (negative control).

### 3.6 Effect of *Citrullus lanatus* rind paste extract on malondialdehyde (MDA) concentration

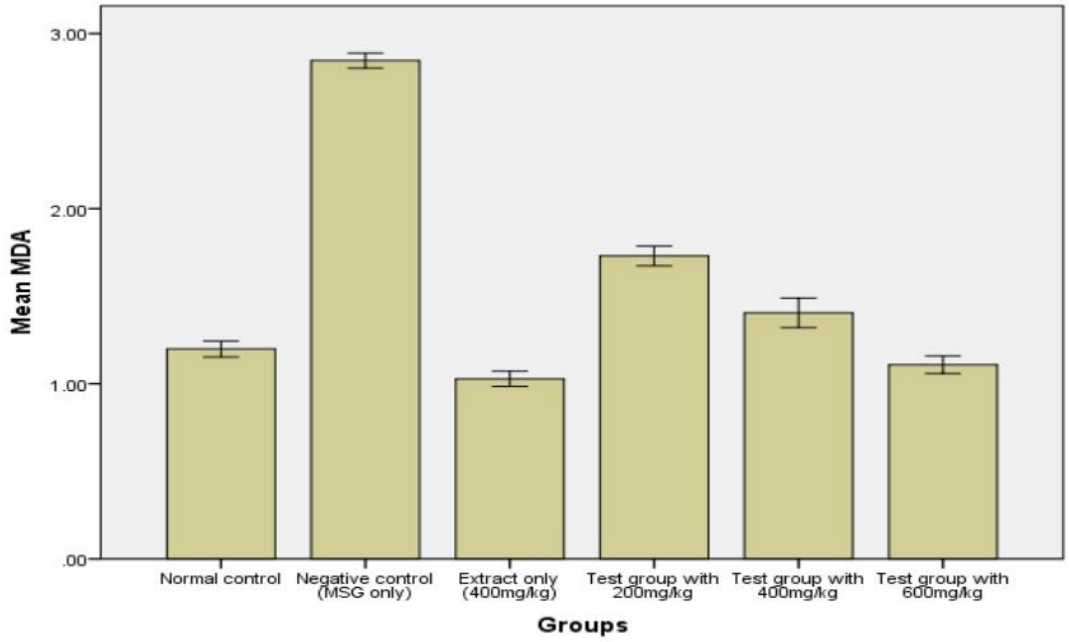


Figure 5: Graph of malondialdehyde (MDA) concentration (μmol/g) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

Figure 5 presents the effect of different doses of *Citrullus lanatus* rind paste extract on MDA level (an index of lipid peroxidation) in hearts of rats. The administration of *Citrullus lanatus* rind paste extract D, E, and F, respectively, significantly ($p<0.05$) decreased MDA activity in the heart of the experimental rats as compared to group B (negative control).

**3.7 Effect of the *Citrullus lanatus* rind paste extract on vitamin C concentration (nmol/L).**

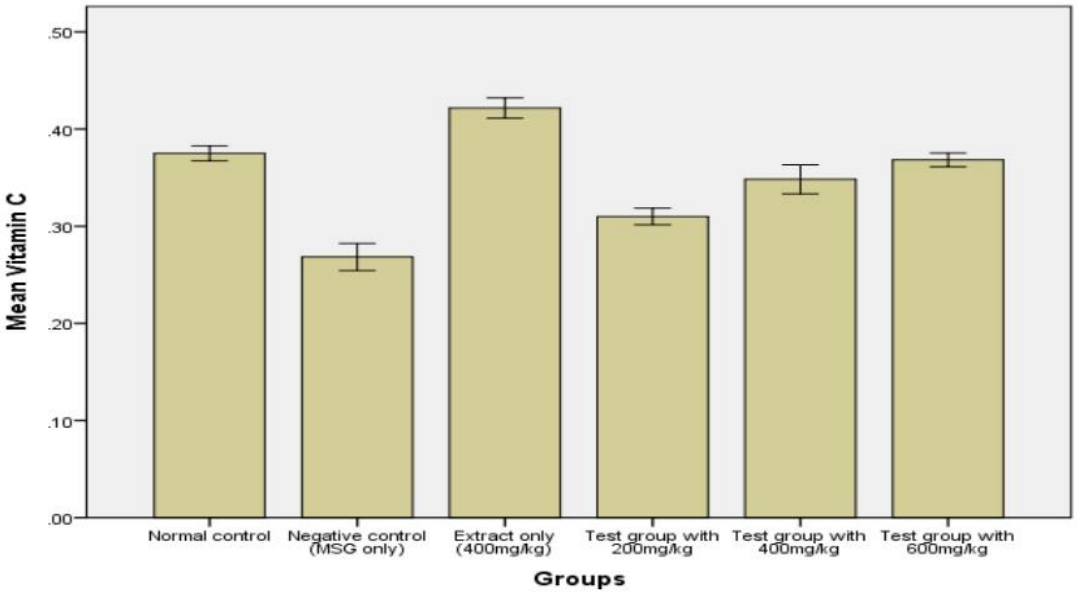


Figure 6: Graph of vitamin C concentration (nmol/l) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

Figure 6 shows significantly ($p<0.05$) increased vitamin C activity in the heart homogenates of the experimental rats C, D, E, and F as compared to the negative control (group B). Group C increased significantly ($p<0.05$) as against group A (normal control), and group B (negative control).

**3.8: Effect of the *Citrullus lanatus* rind paste extract on vitamin E concentration (nmol/L).**

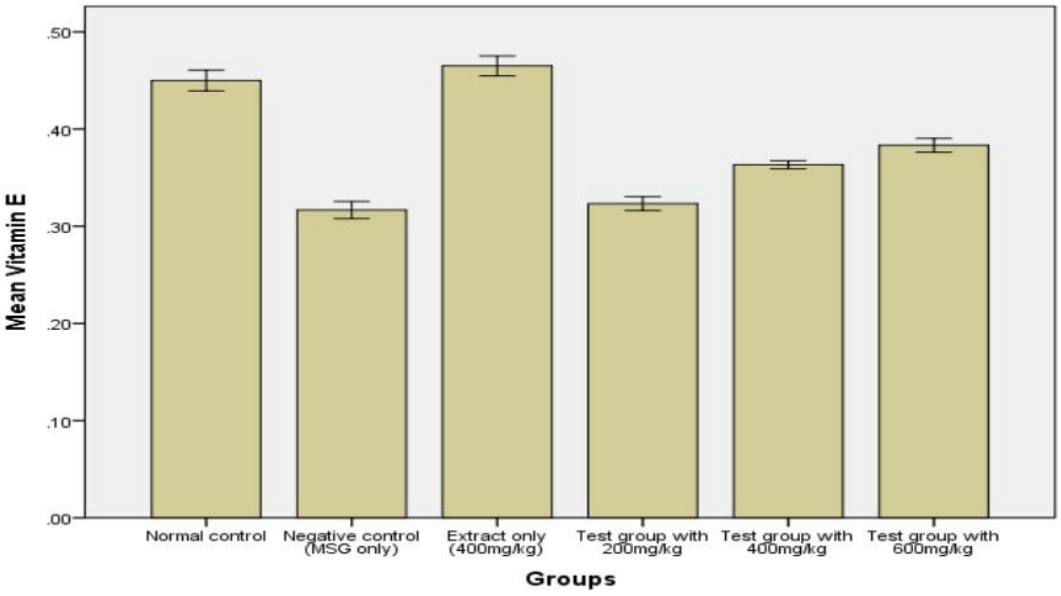


Figure 7: Graph of Vitamin E concentration (nmol/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

There was significantly ($p<0.05$) increase in Vitamin E activity in the heart homogenate of the experimental rats in groups C as against group A (normal control). Groups C, D, E, and F, increased significantly ($p<0.05$) against group B (negative control).

## 4. DISCUSSION

The present investigation confirms that MSG exposure induces oxidative stress in cardiac tissue, as evidenced by increased lipid peroxidation [22,26] and depletion of antioxidant defenses [27,28]. These findings align with earlier report demonstrating ROS-mediated toxicity associated with MSG [6–8,25]. Elevated MDA levels observed in this study reflect enhanced membrane lipid degradation, a hallmark of oxidative injury [22,26]. The concomitant reduction in antioxidant enzymes further indicates impairment of cellular defense systems responsible for detoxifying reactive species [27,28]. Administration of *Citrullus lanatus* rind extract significantly ameliorated these alterations. The restoration of SOD, CAT, GPx, and GSH activities suggests improved redox balance and enhanced enzymatic defense. These effects may be attributed to phytochemicals such as flavonoids and phenolics, which are known to exert strong antioxidant actions [13–15,29]. Additionally, the increase in vitamins C and E levels supports improved antioxidant capacity, as these molecules play critical roles in neutralizing free radicals and protecting cellular membranes [23,30]. The findings align with earlier reports indicating that plant-derived antioxidants can effectively attenuate oxidative stress and improve tissue integrity [31–33].

## 5. CONCLUSION

The results of this study demonstrate that *Citrullus lanatus* rind extract possesses significant antioxidant and cardioprotective properties. The extract effectively mitigates MSG-induced oxidative damage by enhancing antioxidant enzyme activities and reducing lipid peroxidation. These findings highlight the potential utilization of *Citrullus lanatus* rind, an agricultural by-product, as a cost-effective natural antioxidant source. Further studies are recommended to elucidate its molecular mechanisms and clinical relevance

## DECLARATIONS

### Acknowledgments

The author acknowledges the Department of Biochemistry, College of Natural Sciences, Michael Okpara University of Agriculture, Umudike, for providing support for this research. Ethical approval for this study was obtained from the Institutional Animal Ethics Committee of the Michael Okpara University of Agriculture, Umudike, Nigeria. All experimental procedures involving animals were conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

### Ethical approval

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### Conflict of Interest

The author declares no conflict of interest.

### Author Contributions

Freedom M. Aniefiok designed the study, conducted the experiments, analyzed the data, and prepared the manuscript.

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