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Comparative Evaluation of The Antioxidant Activities of *Citrullus lanatus* Rind Extract and Vitamin C in Monosodium Glutamate-Induced Renal Oxidative Stress in Albino Rats

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ABSTRACT

Background: Monosodium glutamate (MSG) has been associated with oxidative stress and renal tissue damage in albino rats. There is growing interest in plant-derived antioxidants as safer and more sustainable alternatives to synthetic compounds such as Vitamin C.

Methods: Thirty-six male albino rats were randomly assigned into six groups (n = 6). Oxidative stress was induced using MSG (8000 mg/kg body weight). Treatment groups received watermelon (*Citrullus lanatus)* rind extract (200, 400, and 600 mg/kg body weight) and Vitamin C for 28 days. Antioxidant biomarkers including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), glutathione peroxidase (GPx), malondialdehyde (MDA), and vitamins C and E were analyzed in kidney tissues using standard biochemical methods.

Results: MSG significantly increased MDA levels and reduced SOD, CAT, GPx, and GSH activities ($p < 0.05$). Treatment with *Citrullus lanatus* rind extract significantly reversed these effects, showing antioxidant activity comparable to Vitamin C.

Conclusion: *Citrullus lanatus* rind extract exhibits significant antioxidant potential and may serve as a natural alternative to Vitamin C in mitigating MSG-induced renal oxidative stress.

Keywords: Antioxidants, Citrullus lanatus, Monosodium glutamate, Oxidative stress, Vitamin C

1. INTRODUCTION

Oxidative stress results from an imbalance between reactive oxygen species (ROS) and antioxidant defense systems [1,7,16-18], leading to cellular damage. Monosodium glutamate (MSG), a widely used food additive, has been reported to induce oxidative stress and organ toxicity when consumed in high amounts [2–4].
Vitamin C is a well-known antioxidant that scavenges free radicals and supports cellular defense systems [6,27,28]. However, interest in plant-derived antioxidants has increased due to their accessibility and diverse phytochemical composition [9-11]. *Citrullus lanatus* (watermelon) rind, often discarded as agricultural waste, contains bioactive compounds such as flavonoids, phenolics, and vitamins with antioxidant properties [13–15]. Despite these properties, its effectiveness relative to standard antioxidants like Vitamin C remains underexplored. Therefore, this study aimed to evaluate the antioxidant potential of watermelon rind extract compared to Vitamin C in MSG-induced oxidative stress in albino rats.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 Biological Materials

Male albino rats (*Rattus norvegicus*)

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2.1.2 Chemicals and Reagents

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

2.1.3 Equipment and Other Materials

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).

2.2 Methods

2.2.1 Preparation of Citrullus lanatus Rind Extract

Fresh *Citrullus lanatus* rinds were washed, air-dried, and homogenized into paste. The paste was soaked in distilled water and allowed to stand for 6-12 hours at room temperature for extraction. The mixture was then filtered using muslin cloth to obtain the rind extract of *Citrullus lanatus*.

2.2.2 Acute Toxicity Study (LD_{50})

Acute toxicity was conducted using Lorke's method [39]. Oral administration of the extract up to 5000 mg/kg body weight produced no mortality, indicating that the extract is relatively safe.

2.2.3 Experimental Design

Thirty-six albino rats (mean weight: 130 g) were divided into six groups (n = 6):

Group A: Control
Group B: MSG (8000 mg/kg body weight) (Negative control)
Group C: Extract only (400 mg/kg body weight)
Group D: MSG (8000 mg/kg) + extract (200 mg/kg body weight)
Group E: MSG (8000 mg/kg) + extract (400 mg/kg body weight)
Group F: MSG (8000 mg/kg) + extract (600 mg/kg body weight)

All treatments were administered orally for 28 days.

The selected dose of MSG (8000 mg/kg body weight) was based on previous studies demonstrating that high-dose MSG reliably induces oxidative stress and organ toxicity in experimental animals [2–4,8]. High-dose MSG models are commonly used to reliably induce oxidative stress and tissue damage within a short experimental period [3,4].

2.2.4 Animal Sacrifice and Tissue Collection

Animals were euthanized under chloroform anesthesia. Kidney tissues were collected, rinsed in saline, homogenized, and used for biochemical assays.

2.2.5 Biochemical Analysis

2.2.5.1 Preparation of Kidney Homogenates

Kidney samples were collected from each rat immediately after blood collection and rinsed in 0.01 M phosphate buffer solution to remove residual blood prior to homogenization. Exactly 0.5 g of each kidney sample was weighed and homogenized using a laboratory mortar and pestle in 0.01 M phosphate buffer solution at a ratio of 1:9 (w/v) (tissue weight to buffer volume). The resulting homogenate was centrifuged at 3,000 rpm for 5 minutes, after which the supernatant was carefully collected and used for subsequent biochemical analyses. 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.

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 anions into molecular oxygen and hydrogen peroxide [22,41]. SOD activity was determined according to the method of

Misra and Fridovich [22], based on the inhibition of adrenaline (epinephrine) auto-oxidation at alkaline pH. In this method, superoxide radicals generated during the auto-oxidation of adrenaline lead to the formation of adrenochrome, which is monitored spectrophotometrically at 480 nm. SOD inhibits this reaction, and the degree of inhibition is proportional to enzyme activity. One unit of SOD activity was defined as the amount of enzyme required to cause 50% inhibition of adrenaline auto-oxidation. In the method, a carbonate buffer (0.05 M, pH 10.2) was prepared. Adrenaline solution was freshly prepared by dissolving 0.01 g of adrenaline in 17 mL of distilled water. An aliquot of the sample (0.1 mL) was added to 2.5 mL of carbonate buffer in a cuvette. The reaction was initiated by the addition of 0.3 mL of freshly prepared adrenaline solution, and the increase in absorbance was immediately monitored at 480 nm at 30-second intervals for 150 seconds. A control was prepared by replacing the sample with distilled water. All assays were carried out in triplicate. SOD activity was expressed as U/mL and calculated from the percentage inhibition of adrenaline auto-oxidation using the formula:

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

where A_0 is the change in absorbance per minute for the control, and A_s is the change in absorbance per minute for the sample.

2.2.6.2 Determination of Catalase (CAT) Activity

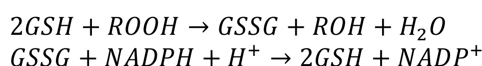
Catalase (CAT) activity was determined according to the method of Aebi (1984) with slight modification and expressed as U/mL of plasma. Catalase catalyzes the decomposition of hydrogen peroxide (H_2O_2) into water and oxygen. The assay is based on the measurement of the rate of decomposition of H_2O_2. In this method, the residual H_2O_2 reacts with dichromate in acetic acid upon heating to form chromic acetate, via an unstable perchromic acid intermediate. The chromic acetate produced is measured spectrophotometrically at 570 nm, and its intensity is inversely proportional to catalase activity. Briefly, the reaction mixture consisted of 2.0 mL of hydrogen peroxide (H_2O_2) solution and 2.0 mL of phosphate buffer (pH 7.0), to which 0.9 mL of distilled water and 0.1 mL of plasma sample were added. The reaction was allowed to proceed for specified time intervals. At each interval, 1.0 mL aliquot of the reaction mixture was withdrawn and the reaction was terminated by adding 2.0 mL of dichromate–acetic acid reagent (prepared in a ratio of 1:3). The tubes were then heated in a boiling water bath for 10 minutes, cooled to room temperature, and the absorbance was measured at 570 nm against a reagent blank. Measurements were taken at 30-second intervals for up to 2 minutes. Catalase activity was expressed as units per milliliter (U/mL), where one unit represents the amount of enzyme required to decompose 1 µmol of H_2O_2 per second under assay conditions. Catalase activity was calculated using the expression:

$$\text{Catalase activity (U/L)} = \frac{0.23 \times \log(\text{Abs}_1/\text{Abs}_2)}{0.00693}$$

Where: Abs_1 = absorbance at time t_1; Abs_2 = absorbance at time t_2

2.2.6.3 Determination of Glutathione Peroxidase (GPx) Activity

Glutathione peroxidase (GPx) activity was determined according to the method of Paglia and Valentine (1967) and expressed as U/L of haemolysate. Briefly, A volume of 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 (pH 7.0) with EDTA, reduced glutathione (GSH), glutathione reductase (GR), and NADPH. The reaction was initiated by the addition of cumene hydroperoxide. The initial absorbance of both test and reagent blank was recorded at 340 nm after 1 minute, and the timer was started simultaneously. Absorbance readings were then taken at 1-minute intervals for 2 minutes. Reactions involved were as follows



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

Glutathione peroxidase activity was calculated from the rate of decrease in absorbance at 340 nm and expressed as:

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

Where: $\Delta A_{340}/\text{min}$= change in absorbance per minute at 340 nm.

2.2.6.4 Determination of reduced glutathione (GSH) activity.

A volume (0.2 mL) of sample was mixed with 1.8 mL of EDTA solution. To this 3.0 mL of precipitating reagent was added, mixed thoroughly and kept for 5 min before centrifugation. To 2.0 mL of the supernatant, 4.0 mL of

0.3 M disodium hydrogen phosphate solution and 1.0 mL of DTNB reagent were added and the colour developed was read at 412 nm in spectrophotometer. A set of standard solutions containing 20–100 mg of reduced glutathione was treated similarly. The values were expressed as mg/dL for plasma.

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 [38]. 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 (1.56×10^5 $L \cdot mol^{-1} \cdot cm^{-1}$) using the formula:

$$A = \varepsilon CL,$$

where A = absorbance, ε = molar coefficient, C = concentration and L = path length. TBARS concentration was expressed in µmol/g tissue protein.

2.2.7.2 Determination of vitamin C concentration

Vitamin C (ascorbic acid) concentration was determined according to the method of Emadi-Konji et al. [49].

1.0 mL of the sample was transferred into a test tube, followed by the addition of 1.0 mL of 10% trichloroacetic acid (TCA) for protein precipitation. Subsequently, 0.5 mL of chloroform was added, and the mixture was shaken vigorously for 15 seconds. The mixture was then 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. The blank and standard were prepared by mixing 0.5 mL of 10% TCA with 0.5 mL of distilled water (blank) or 0.5 mL of working standard solution (standard), respectively. To each test tube (sample, blank, and standard), 0.4 mL of freshly prepared combined color reagent was added. The tubes were stoppered, mixed thoroughly, and incubated in a water bath at 56°C for 60 minutes. After incubation, the tubes were cooled in an ice bath for approximately 5 minutes. Thereafter, 2.0 mL of ice-cold 85% sulfuric acid was added slowly with continuous mixing. The tubes were allowed to stand at room temperature for 30 minutes for full color development. The absorbance (optical density) of the sample and standard solutions was measured at 490 nm against the blank using a spectrophotometer.

Vitamin C concentration was calculated using the expression:

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

Given that the standard concentration = 2.0 mg/100 mL:

$$\text{Vitamin C (mg/100 mL)} = \frac{A_{\text{sample}} \times 2.0}{A_{\text{standard}}}$$

2.2.7.3 Determination of vitamin E concentration

Vitamin E analysis was done according to the method of Wei, [50].

A portion (150 mg) of Na_2SO_4 was placed in a test tube and put in a desiccator to avoid moisture. About 100 µL of the sample was put into the test tube using an automatic pipette and the tip of the pipette rinsed with distilled water each time after use. A portion (2.0 mL) of acetone was added and the mixture was shaken vigorously to denature the proteins. About 500 µL internal standard solution was added to the test tube, shaken, and allowed to stand for 2 h. The test tube was centrifuged for 20 min. Using a Pasteur pipette the supernatant was collected and transferred to a syringe connected to a 0.45 µm filter. The test tube was rinsed with 1.5 mL of acetone and transferred into the syringe and filtered again. The mixture was evaporated gently at 40°C. The dry tube was capped and put in ice for 2 min. Cm (1:3 w/BHT) mixture flask was also put in the ice. 500 µL of CM mixture was added into another test tube and the tube was vortexed 3 times. The tube was wrapped and placed to stand for 2 h in the freezer. A portion (50 µL) of the final solution was injected into the HPLC system and ran for 6 min 30 s. Degassed methanol was used as the mobile phase with a flow rate of 2 mL/min. Detection was monitored at 292 nm. The linear range of α-tocopherol standard curve was from 50–500 ng (r = 0.999).

2.2.7.4 Determination of melatonin concentration

Melatonin concentration was determined following the extraction procedure described in [51]. Serum and dichloromethane were combined in a 1:5 (v/v) ratio and mixed gently for 30 s. The mixture was then centrifuged at 2000 × g at 4°C for 20 min. The upper phase was carefully removed without disturbing the dichloromethane phase. For smaller volume samples, the upper phase was not removed, and the tubes were placed directly on dry ice. The dichloromethane phase was subsequently transferred into a new glass tube and evaporated to dryness using a SpeedVac concentrator (Savant Instruments). An equal volume of assay buffer, corresponding to the original serum volume, was added to the dried residue and mixed thoroughly prior to analysis.

2.3 Statistical Analysis

Data were expressed as mean ± standard deviation. One-way ANOVA was used for analysis, with significance accepted at $p < 0.05$.

3. RESULTS

MSG administration significantly increased MDA levels ($p < 0.05$), indicating elevated lipid peroxidation. Antioxidant enzymes (SOD, CAT, GPx, GSH) were significantly reduced in the MSG-treated group. Treatment with *Citrullus lanatus* rind extract resulted in dose-dependent restoration of antioxidant enzymes and a reduction in MDA levels. The extract demonstrated antioxidant effects comparable to vitamin C. No mortality was recorded in the acute toxicity study, confirming the safety of the extract at tested doses.

3.1 Effect of the *Citrullus lanatus* rind extract on glutathione peroxidase (GP_X) activity (U/L)

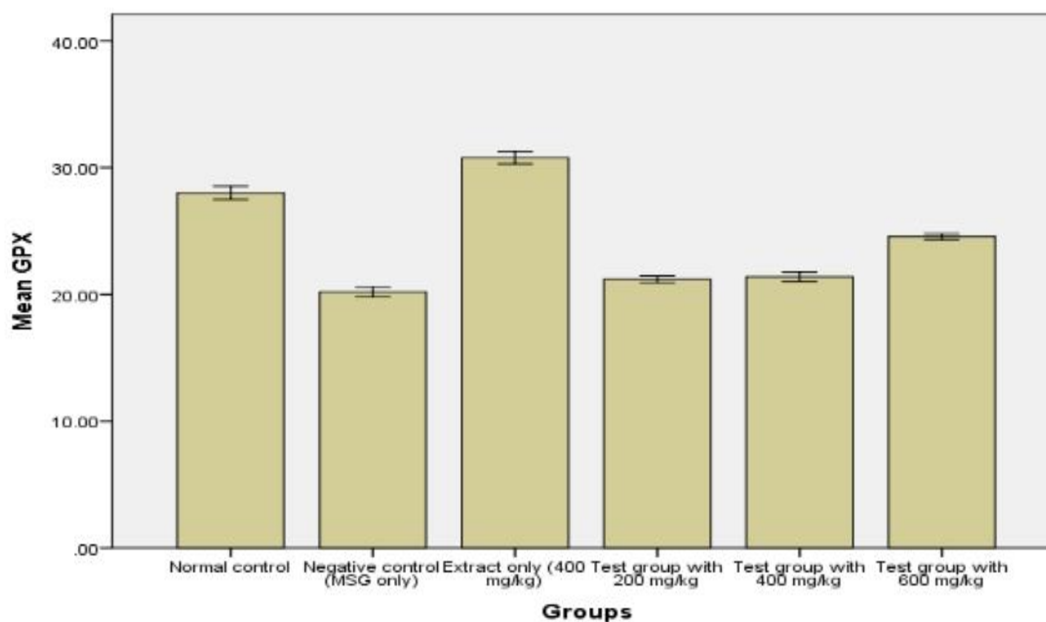


Figure 1: Graph of glutathione peroxidase (GP_X) activity (U/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

Figure 1 shows the GPX activity in kidney homogenate of the experimental rats. There was significant ($P<0.05$) increase in GPX activity in rats that were administered oral doses of *Citrullus lanatus* 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).

3.2 Effect of the *Citrullus lanatus* rind paste extract on Reduced Glutathione (GSH) activity (U/L).

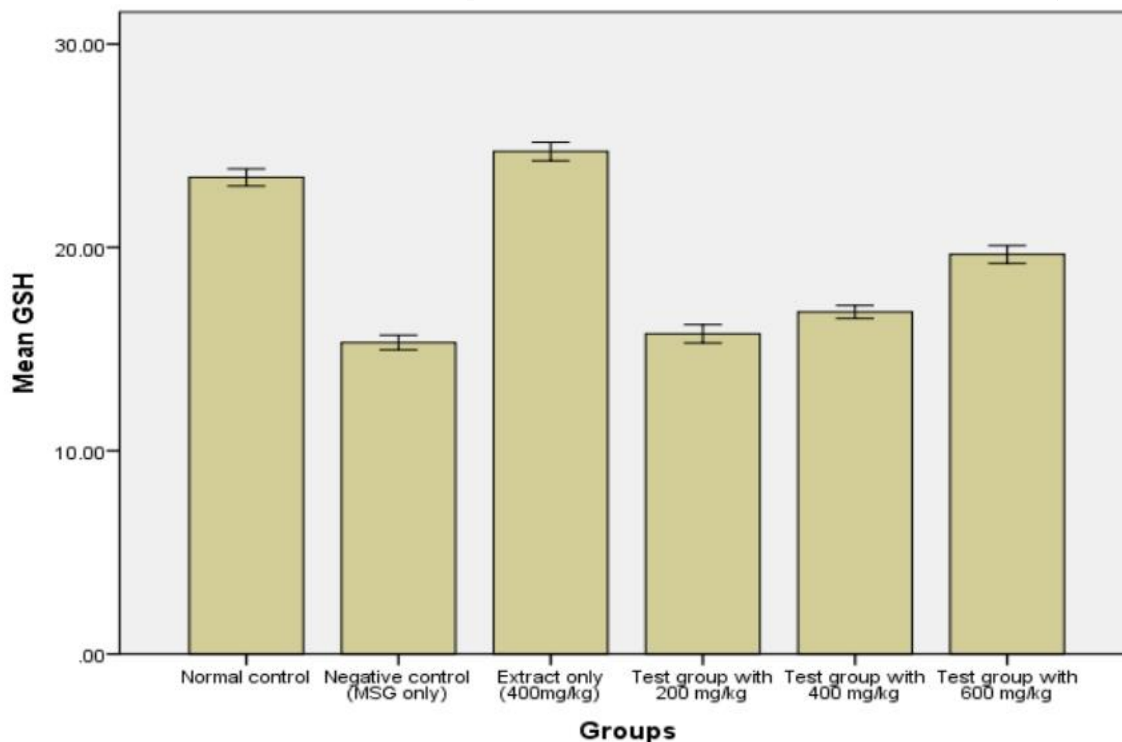


Figure 2: Graph of Reduced Glutathione (GSH) activity (U/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

Figure 2 shows the effect of different doses of watermelon rind paste extract on reduced glutathione (GSH) concentration in the experimental rats. There was a significant ($p < 0.05$) increase in GSH level in kidney homogenate of rats given graded doses of *Citrullus lanatus* rind paste extract in groups D, E, and F (200, 400, and 600 mg/kg body weight respectively) compared with the negative control (group B).

3.3 Effect of *Citrullus lanatus* rind extract on superoxide dismutase (SOD) activity (U/L)

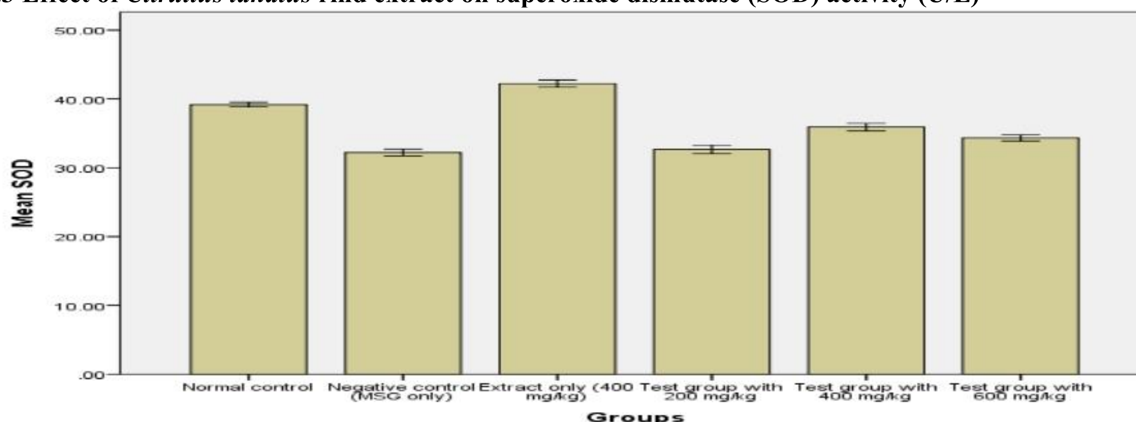


Figure 3: Graph of Superoxide Dismutase (SOD) activity (U/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

Figure 3 shows that the oral administration of *Citrullus lanatus* rind paste 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 kidneys of the experimental rats as compared to the negative control (group B), and remained lower in group A (normal control).

3.4: Effect of *Citrullus lanatus* paste extract on catalase (CAT) activity (U/L)

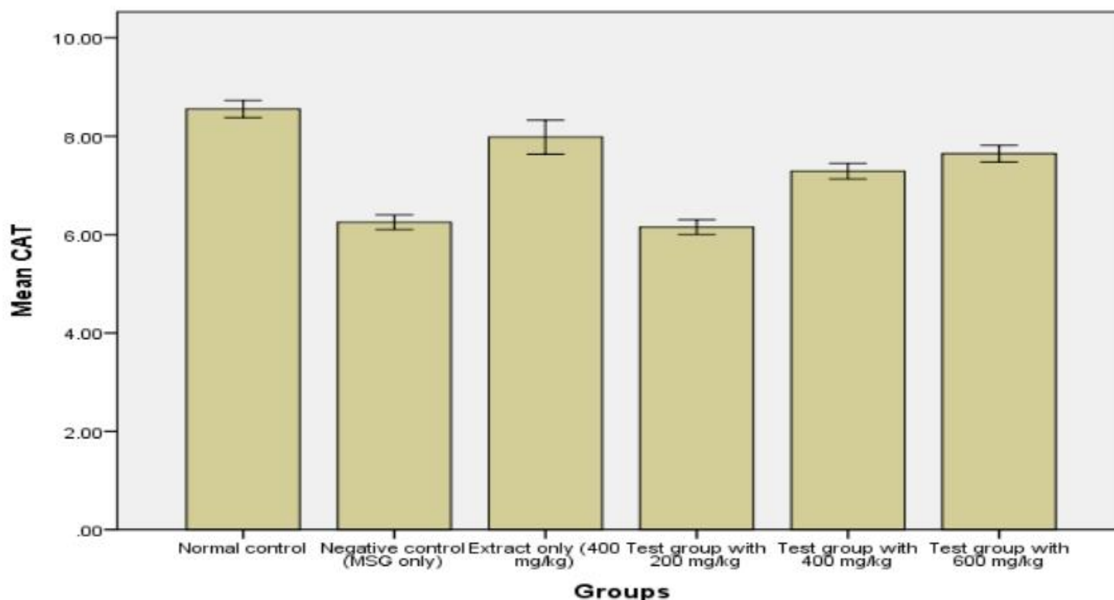


Figure 4: Graph of catalase (CAT) activity (U/L) of rats intoxicated with monosodium glutamate (MSG) and treated with Citrullus lanatus rind paste extract.

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

3.5 Effect of *Citrullus lanatus* rinds extract on malondialdehyde (MDA) concentration (μmol/g).

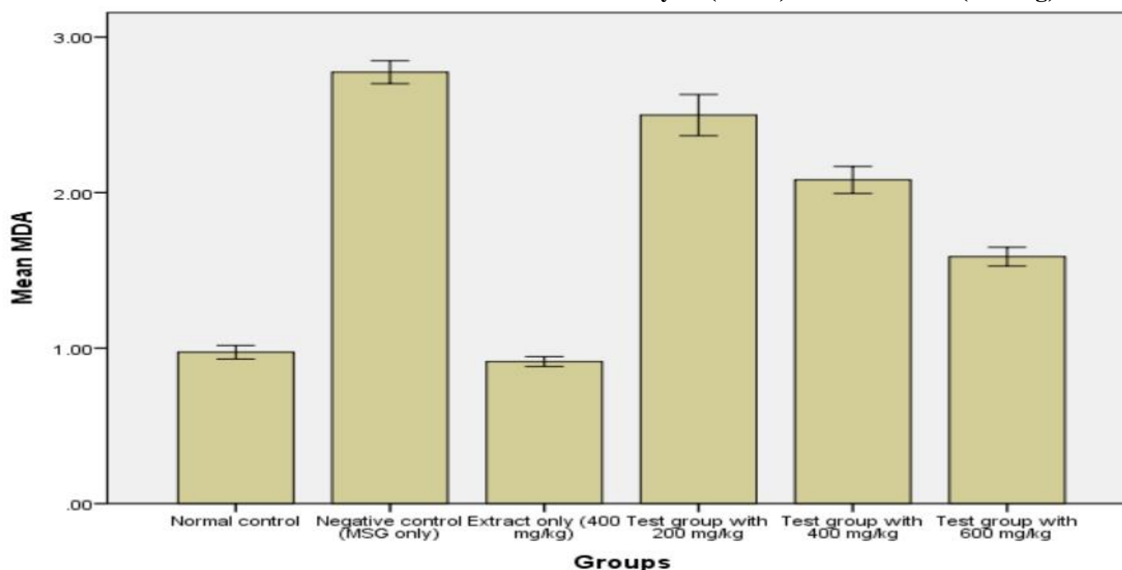


Figure 5: Graph of malondialdehyde (MDA) concentration (µmol/g) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

MDA level (an index of lipid peroxidation) in kidneys of rats as presented in Fig 5. The administration of *Citrullus lanatus* rind paste extract orally at the doses of 200, 400, and 600 mg/kg body weight in groups D, E, and F, respectively, significantly ($p<0.05$) decreased MDA activity in the kidneys of the experimental rats. MDA activity decreased significantly ($p<0.05$) in groups A, C, D, E, and F, when compared to group B (negative control).

3.6 Effect of *Citrullus lanatus* rind paste extract on Vitamin C concentration (nmol/L).

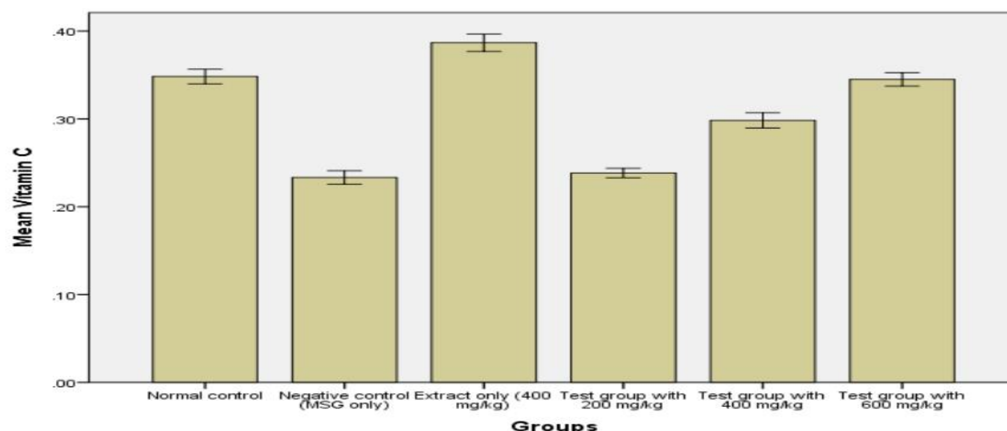


Figure 6: Graph of Vitamin C concentration (nmol/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract

Figure 6 shows significantly increased Vitamin C concentration in the kidneys of the experimental rats C, D, E, and F (group given extract only at 400 mg/kg, group given 200 mg/kg, group given 400mg/kg and group given 600 mg/ kg body weight respectively) as compared to the negative control (group B).

3.7 Effect of *Citrullus lanatus* rind paste extract on Vitamin E concentration (nmol/L).

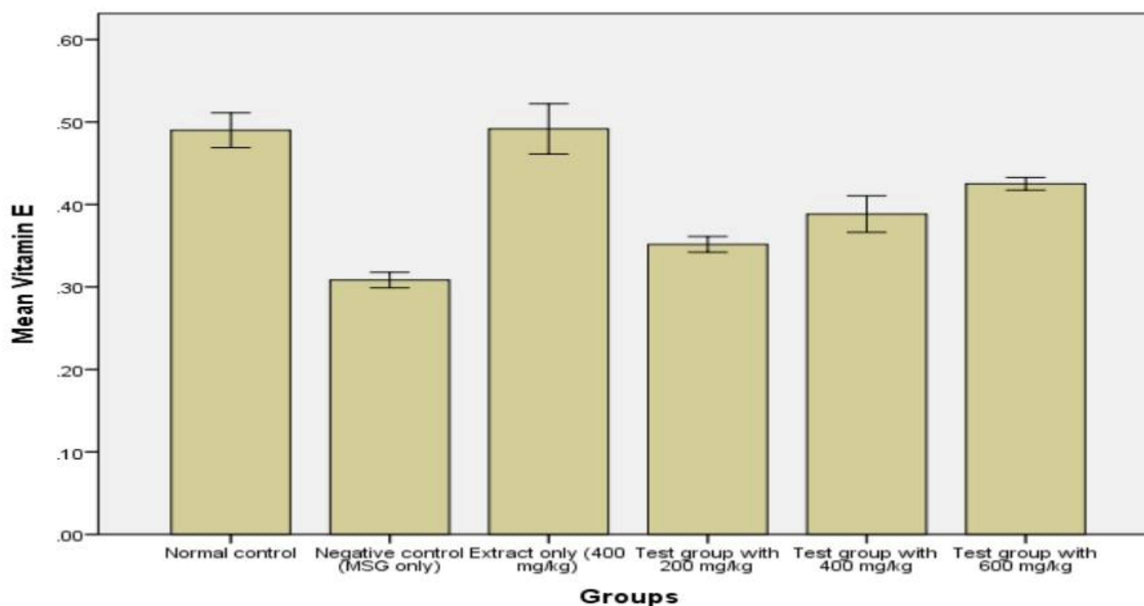


Figure 7: Graph of Vitamin E concentration (nmol/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

There was significantly ($p<0.05$) increase in Vitamin E activity in the kidney homogenate of the experimental rats in groups given doses of 200, 400, and 600 mg/kg body weight as compared to the negative control (group B) as shown in Fig 7.

3.8 Effect of *Citrullus lanatus* rind paste extract on Melatonin (nmol/L).

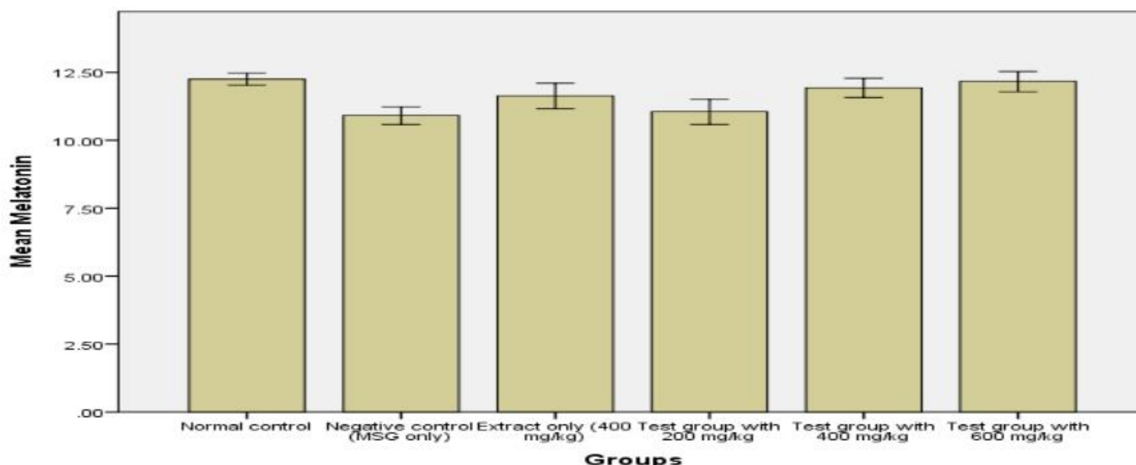


Figure 8: Graph of melatonin concentration (nmol/L) of rats intoxicated with monosodium glutamate (MSG) and treated with *Citrullus lanatus* rind paste extract.

Figure 8 shows Melatonin concentration in kidneys homogenates of the experimental rats. There was a significant increase in Melatonin concentration in rats administered oral doses of *Citrullus lanatus* rind extract at 200 (group D), 400 (group E) and 600 (group F) mg/kg body weight compared with negative control (group B).

4. DISCUSSION

The results obtained in this study show that MSG induces oxidative stress, as evidenced by increased lipid peroxidation and decreased antioxidant enzyme activity [2,4]. These findings are consistent with previous reports indicating that MSG induces oxidative stress through excessive generation of reactive oxygen species and disruption of antioxidant defense systems [16-18]. Vitamin C significantly improved antioxidant status, confirming its established role as a potent free radical scavenger. It acts by donating electrons to neutralize reactive species and regenerating other antioxidants within biological systems [6,23–25]. Interestingly, *Citrullus lanatus* rind extract exhibited comparable and, in some cases, superior antioxidant effects relative to Vitamin C. This may suggest that the phytochemical composition of the rind may provide synergistic antioxidant activity [9–11,13–15]. Compounds such as flavonoids and phenolics are known to enhance antioxidant defense mechanisms and inhibit lipid peroxidation [9,13]. The reduction in MDA levels observed with rind extract treatment indicates decreased membrane lipid damage, while the restoration of SOD, CAT, GPx, and GSH suggests improved cellular defense systems. These findings align with studies reporting strong antioxidant effects of plant-derived compounds with well-documented antioxidant properties [9–11,30]. The comparative advantage of *Citrullus lanatus* rind may be attributed to its multi-component antioxidant system, unlike Vitamin C, which functions primarily as a single-molecule antioxidant. This multi-target mechanism may explain its enhanced effectiveness particularly due to flavonoids and other reactive oxygen scavenging compounds [6,27,28]. Furthermore, the use of *Citrullus lanatus* rind as a natural antioxidant offers economic and environmental benefits by converting agricultural waste into valuable health products.

5. CONCLUSION

Watermelon rind (*Citrullus lanatus*) extract exhibits significant antioxidant activity comparable to Vitamin C in mitigating MSG-induced oxidative stress. The extract effectively restores antioxidant enzyme levels and reduces lipid peroxidation. These findings highlight the potential of watermelon rind as a natural, cost-effective alternative to synthetic antioxidants. Its application in nutraceutical development and disease prevention warrants further investigation. Further studies should explore the molecular mechanisms and clinical applicability of watermelon rind extract in oxidative stress-related disorders.

DECLARATIONS

Acknowledgment

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Ethical approval

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.

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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