

## **Histopathological Evaluation of Organs of Male Wistar Rats Fed with Monosodium Glutamate Treated-diet**

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### **Authors' contributions**

*This work was carried out in collaboration with all authors. Author EOO conceptualized designed and also managed the analyses of the study. Author AIA managed the literature searches and also wrote the manuscript. Author UO wrote the protocol and performed the statistical analysis. All authors read and approved the final manuscript.*

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### **ABSTRACT**

**Background:** Recently, the use of seasonings to enhance the flavour of food has increased. A variety of seasonings are produced nowadays and the constituents of these flavour-enhancers are unknown to ignorant consumers. Most consumers preferred to eat food with good taste without considering the effect of additives on their health. One of the most commonly used food additives is monosodium glutamate that is widely used as a food seasoning.

**Aim:** This study sought to evaluate the histopathological changes in Wistar rats fed with monosodium glutamate treated-diet.

**Place:** This research was carried out at the Department of Pharmacology and Therapeutics, College of Medicine and Health Sciences, Abia State University, Uturu, Nigeria in 2011.

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**Methods:** MSG (3 g/sachet containing 99% MSG) was obtained from a Grocery Store at New Market, Aba in Abia State, Nigeria. Forty Wistar rats were used for this study. Fifteen of the rats were used for acute toxicity test ( $LD_{50}$ ) and twenty-five for the experiment. The 25 Wistar rats were divided into five groups of 5 rats each. Animals in groups A, B, C, and D were respectively administered 500 mg/kg, 750 mg/kg, 1,000 mg/kg and 1,250 mg/kg of MSG thoroughly mixed with standard feed for eight weeks. Animals in group E received an equal amount of feeds without MSG added. This group served as the control group. At the end of 8 weeks, animals were humanely sacrificed and organs were harvested.

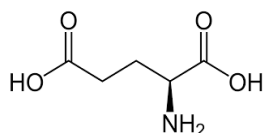
**Result:** The  $LD_{50}$  was taken to be 500 mg/kg, which is the median of 200 mg/kg which did not kill any of the animals and 800 mg/kg that killed all its animals. The histopathology of the testes, liver, spleen, heart, lungs and kidneys were evaluated. Treatment with MSG was observed to cause necrosis in the organs investigated.

**Conclusion:** The results of this study showed that MSG is toxic to organs of the animals used and its use as flavour enhancer should be discouraged.

**Keywords:** Monosodium glutamate; testes; liver; spleen; heart; lungs; kidneys.

## 1. INTRODUCTION

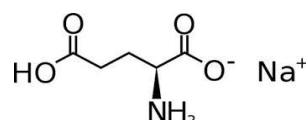
Monosodium glutamate (MSG) is a sodium salt of glutamic acid. It is usually a white powder. Water ionizes it into free sodium ions and glutamic acid, which is an organic compound consisting of five carbon atoms [1]. It has a carboxylic (-COOH) group and an amino (-NH<sub>2</sub>) group attached to an "alpha" carbon atom (a carbon atom joined directly to the -COOH group). It is an alpha-amino acid. The molecular formula of MSG is C<sub>3</sub>H<sub>8</sub>NNaO<sub>4</sub> and its molecular mass is 169.11g/mol<sup>-1</sup>. MSG has the same basic structure of amino acids, with an amine group (-NH<sub>2</sub>) and carboxylate ion instead of the carboxylic group (-COO<sup>-</sup>). MSG has the almost same structure with glutamate. The difference is that one hydrogen atom at the carboxylic chain has been replaced with a sodium atom, hence, the name monosodium glutamate [1].



**Fig. 1. Structure of glutamate [2]**

Monosodium glutamate has a distinctive taste that falls outside the region of the four classic tastes: sweet, sour, salty, and bitter. This taste is called "Umami," also referred to as "Xien Wei" in Chinese or "savory," "broth-like" or "meaty taste" in English. Due to this special taste, many food producers use MSG to enhance the flavour of their product [3]. Recently, Chaudhari et al. [4] identified a specific glutamate taste receptor on the tongue. Three umami substances (glutamate, 5-inosinate, and 5-guanylate) were found by Japanese scientists, but umami has not been

recognized in Europe and America for a long time. In the late 1900s, umami was internationally recognized as the fifth basic taste based on psychophysical, electrophysiological, and biochemical studies. Three umami receptors (T1R1 + T1R3, mGluR4, and mGluR1) were identified. There is a synergism between glutamate and the 5-nucleotides. Among the above receptors, only T1R1 + T1R3 receptor exhibits the synergism [5]. Since glutamate and 5-inosinate are contained in various foods, umami taste is induced by the synergism in daily eating [5].

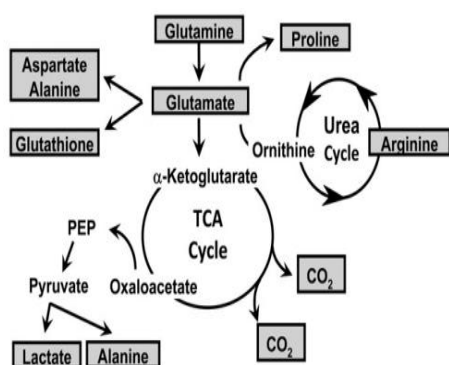


**Fig. 2. Structure of monosodium glutamate [2]**

The safety and toxicity of MSG had become controversial in the last few years due to reports of adverse reactions in people who have eaten foods that contain MSG. Many studies had confirmed the adverse reactions of MSG [1,6,7].

MSG has been reported to cause headache, vomiting, diarrhoea, irritable bowel syndrome, asthma attacks in asthmatic patients and panic attacks [1]. Obuchi et al. [7] studied the effect of garlic extracts on MSG induced fibroid in Wistar rats and reported that MSG alone can increase total protein, cholesterol and estradiol (estrogen), which in turn, induced fibroid in the rats. However, treatment with garlic extracts near-completely abrogated/mitigated any effects that have been induced by MSG alone. Egbuonu et al. [8] endorsed that investigating the potentials of low concentration administration of

monosodium glutamate in inducing hepatotoxicity in male albino rats. In that study, it was observed that treating rats with monosodium glutamate at a low concentration (5 mg/kg of body weight) could be hepatotoxic without significant cholestasis or pathologies of the bone. Onyema et al. [9] reported that MSG at a dose of 0.6 mg/g body weight induced the oxidative stress and hepatotoxicity in rats and vitamin E ameliorated MSG-induced oxidative stress and hepatotoxicity. Meraiyebu et al. [10] reported that MSG increased the number of platelets, bleeding time and clotting time in MSG-treated rats. Onyema et al. [11] tested the hypothesis that alteration in glucose metabolism following MSG administration might be a contributor to the changes in the markers of oxidative stress observed in the animals [2]. The pattern of induction of oxidative stress and alteration of glucose metabolic enzymes in the animals was an indication that oxidative stress induced by MSG in the renal tissues of rats might be contributed by increased tissue glucose concentration resulting from enhanced renal gluconeogenesis [2,11]. Nwajei et al. [12] reported that four selected food seasonings (labelled IS, KC, SMC and BS) commonly consumed in Nigeria adversely perturbed some sex hormones: testosterone, estrogen and progesterone of Wistar albino rats due to the presence of MSG in these seasonings. Kolawole [13] investigated the effect of orally administered MSG on food consumption, body weight and some biochemical and haematological parameters in adult Wistar rats and reported that MSG at the doses of 5 – 15 mg/kg body weight was not hazardous to health. Furthermore, Ogbuagu et al. [14] have previously reported that MSG has a hyperglycemic and hypocholesterolemic effect on Wistar rats. MSG has also been reported to increase weight gain as well as induced hepatotoxicity [15].



**Fig. 3. Metabolic fates of dietary glutamate in the intestine [2]**

## 2. MATERIALS AND METHODS

### 2.1 Collection of Monosodium Glutamate

The Monosodium Glutamate (3g/sachet containing 99% MSG) was obtained from a Grocery Store at New Market, Aba in Abia State, Nigeria.

### 2.2 Collection of Animals

Forty (40) adult Wistar rats with a body weight between 160 and 200 g were obtained from the animal house of the Department of Pharmacology and Therapeutics, College of Medicine and Health Science, Abia State University, Uturu, Nigeria. They were acclimatized for seven days before the study. All the animals were handled following the standard guidelines for care and use of laboratory animals. The animals had access to standard animal feed purchased from a local commercial supplier and water *ad libitum* and housed under a standard condition of temperature ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}$ ) under 12 hours light-darkness cycles. Fifteen (15) of the rats were used for acute toxicity test and twenty-five (25) for the experiment.

### 2.3 Acute Toxicity Test (LD<sub>50</sub> Determination)

The acute toxicity test (LD<sub>50</sub>) was determined using a modified version of the method proposed by Lorke [16] which involves the use of the minimal number of experimental animals. This method of acute toxicity determination makes the following assumptions.

- I. Substances more toxic than 1 mg/kg body weight are so highly toxic that it is unnecessary to calculate the LD<sub>50</sub>.
- II. LD<sub>50</sub> values greater than 5000 mg/kg are of no practical interest.
- III. An approximate figure for the LD<sub>50</sub> is usually adequate to estimate the risk of acute intoxication.

The LD<sub>50</sub> is taken as the median concentration that killed 50% of the test animals. The median lethal dose was estimated as the geometric mean of the least dose at which none of the animals died and the highest concentration at which all the animals died. The 15 animals used for determination of LD<sub>50</sub> were divided into five groups of 3 each. Groups A, B, C and D were administered 100 mg/kg, 200 mg/kg, 400 mg/kg and 800 mg/kg of MSG respectively through the intraperitoneal route of drug administration while

group E was similarly treated but with a saline solution. This group served as the control group. The animals were constantly observed for 24 hours for signs of toxicity and death.

## 2.4 Experimental Design

A total of 25 adult Wistar rats were divided into five groups of 5 rats each. Animals in groups A, B, C, and D were respectively administered 500 mg/kg, 750 mg/kg, 1,000 mg/kg and 1,250 mg/kg of MSG thoroughly mixed with standard feed for 8 weeks. Animals in group E received an equal amount of feeds but without MSG. This group served as the control group. At the end of 8 weeks, animals were sacrificed and organs (testes, liver, spleen, heart, lungs and kidneys) were harvested.

## 2.5 Histological Preparations

The organs were cut to sizes of about 0.5cm thick on a slab and fixed in Bouin's fluid for about 24 hours and transferred to ascending alcohol concentration for dehydration. Each piece was directly put into 70% alcohol for six hours and then transferred to 90% alcohol where they stayed overnight. They were later transferred to 3 changes of absolute alcohol for one hour each and then put into chloroform for 10 hours and fresh chloroform for another 30 minutes. The tissues were placed vertically in molten paraffin wax inside a metal mould and left overnight to cool and solidify. They were trimmed and mounted on wooden blocks. Serial sections of 6 microns thick were obtained using a rotatory microtome. The deparaffinized sections were stained routinely with haematoxylin and eosin. Photomicrographs of desired sections were made for further observations.

## 2.6 The technique for Staining with Mayer's Acid-Alum-Haematoxylin and Eosin

- ✓ The slides were put in staining rack and placed in staining wells containing xylene to dewax.
- ✓ They were hydrated by transferring into two changes of absolute alcohol: 70% of alcohol and in water for 5 minutes.
- ✓ The slides were stained in Mayer's acid-alum-haematoxylin solution for 10 – 30 minutes.

- ✓ They were washed thoroughly in running acid alcohol.
- ✓ The slides were differentiated with 1% acid alcohol
- ✓ Sections were placed in running tap water for 5 – 10 minutes to blue.
- ✓ The sections were counterstained in 1% eosin and washed with water to remove excess eosin.
- ✓ They were dehydrated with 70%, 90% and absolute alcohol as well as xylene to remove all traces of water.
- ✓ A drop of the mountant, polystyrene dibutyl phthalate xylene (DPX) was placed on the surface of the slide, covered with a coverslip and then mounted.

## 2.7 Constituents of Mayer's Acid-Alum-Haematoxylin

Ammonium – alum	50 g
Chloral hydrate	50 g
Haematoxylin	1 g
Citric acid	1 g
Sodium iodates	0.2 g
Distilled water	1000 ml

## 3. RESULTS

### 3.1 Acute Toxicity Test

One of the animals in Group D (administered 800 mg/kg body weight) died within the first 30 minutes of administration. After 12 hours of observation, another one died in Group D. The remaining one in group D and one in group C died overnight. The LD<sub>50</sub> was then taken to be 500 mg/kg, which is the median of 200 mg/kg which did not kill any of the animals and 800 mg/kg that killed all its animals.

### 3.2 Systemic Effect of MSG

Two weeks into the study, most of the animals in the experimental group became hyperactive. Four, weeks later, one of the animals in the group fed with 1,250 mg/kg of MSG developed bulging of eyeballs (exophthalmos), and had several bouts of seizures before its demise six days later.

### 3.3 Effects of MSG on the Histological Sections of the Testis

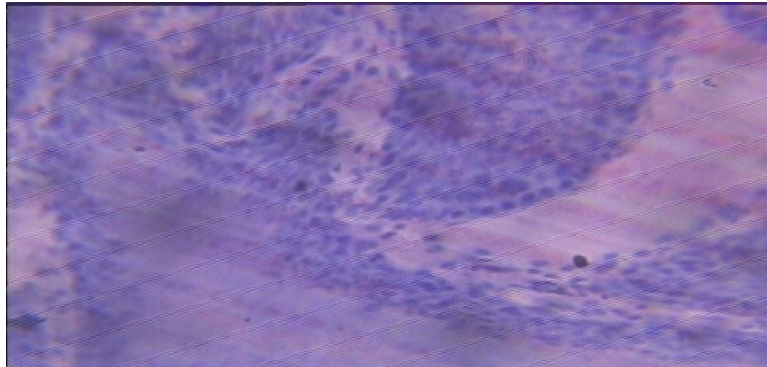
Feeding of animals with MSG treated-diet led to a reduction in spermatocytes, Patchy areas of necrosis, and scanty seminiferous tubules.

### 3.4 Effects of MSG on the Histological Sections of the Liver

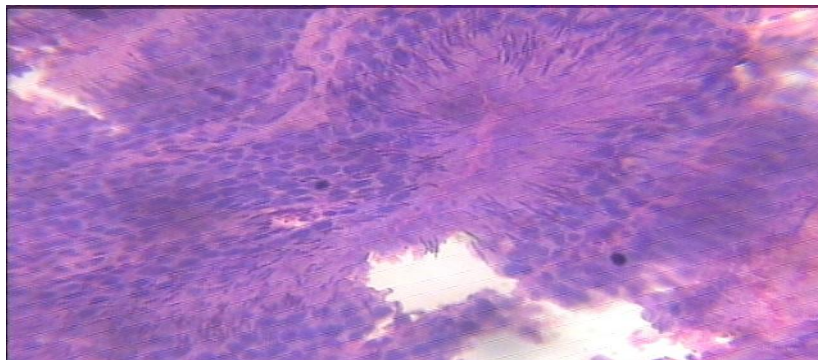
Feeding of animals with MSG treated-diet resulted in massive and generalized necrosis in the liver, with little area of regeneration. Surviving areas were scanty and had cells with clumped nuclei.

### 3.5 Effects of MSG on the Histological Sections of the Spleen

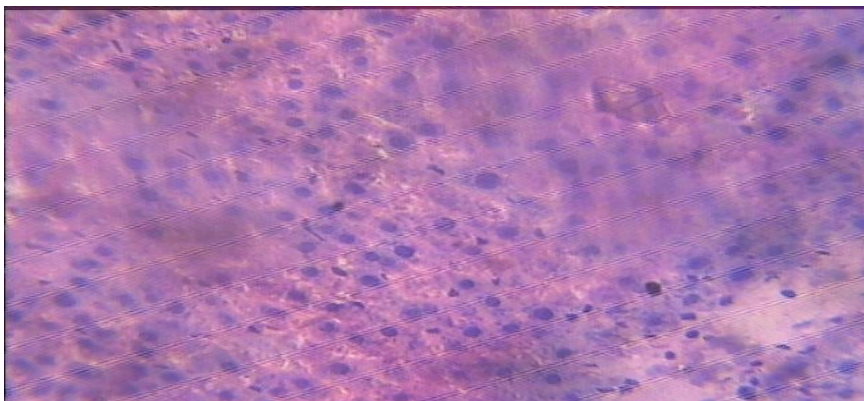
Feeding of animals with MSG treated-diet led to generalized fatty change. Surviving areas had massive inflammatory infiltrates and hypertrophy. There were also edematous degenerative changes at the medulla and pulp.



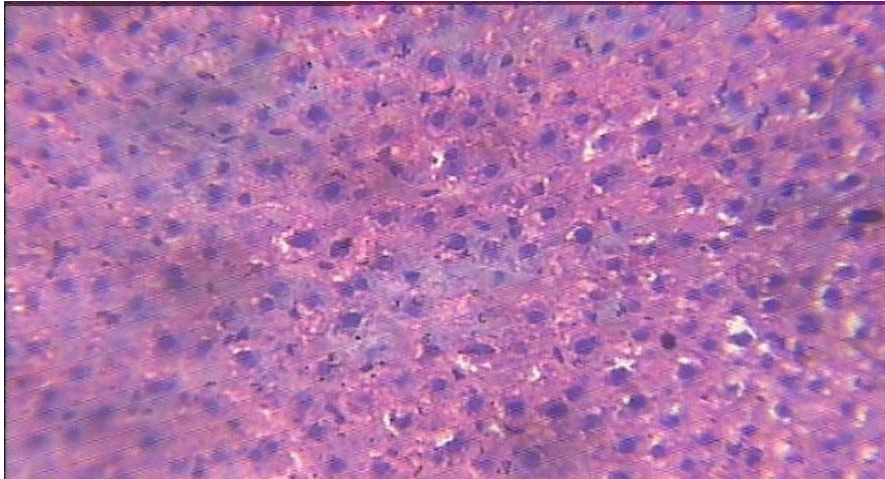
**Fig. 4. Photomicrograph of the section of testis in the control group which shows normal testicular cells with dilatation of ducts (ectasia). Mag. X 100(H&E)**



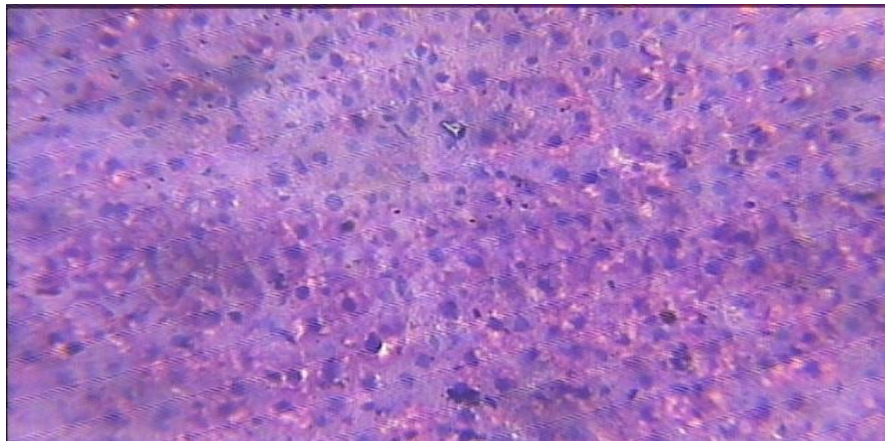
**Fig. 5. Photomicrograph of the section of the testis of the rat fed with 1000 mg/kg of MSG, which showed a reduction in spermatocytes, Patchy areas of necrosis, and scanty seminiferous tubules. Mag. X 80(H&E)**



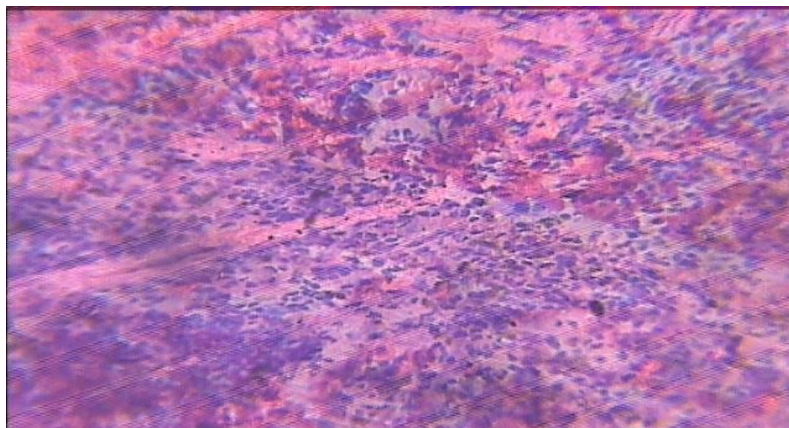
**Fig. 6. Photomicrograph of the section of the liver in the control group which shows normal hepatocytes and patchy monocytic infiltrates. Patchy areas of necrosis are quite a few. Mag. X 80(H&E)**



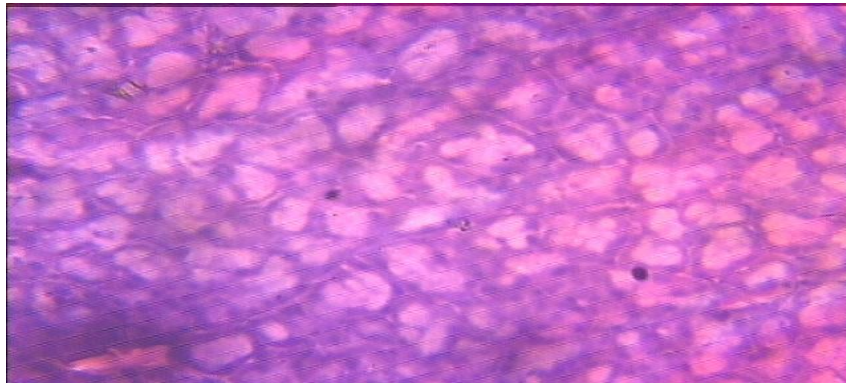
**Fig. 7. Photomicrograph of the liver of the rat fed with 1000 mg/kg of MSG, which showed massive and generalized necrosis, with little area of regeneration. Surviving areas are scanty and have cells with clumped nuclei. Mag.X100 (H&E)**



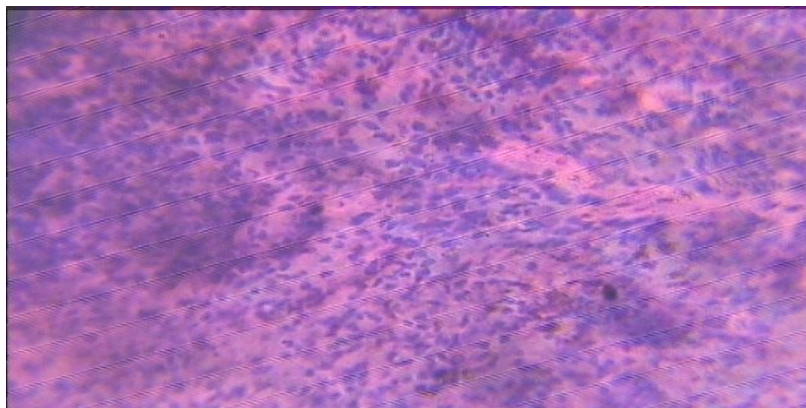
**Fig. 8. Photomicrograph of the section of the liver of the rat fed with 1250mg/kg of MSG, which showed distortion of the entire liver architecture. There are total necrosis and loss of hepatocytes. Mag. X 90(H&E)**



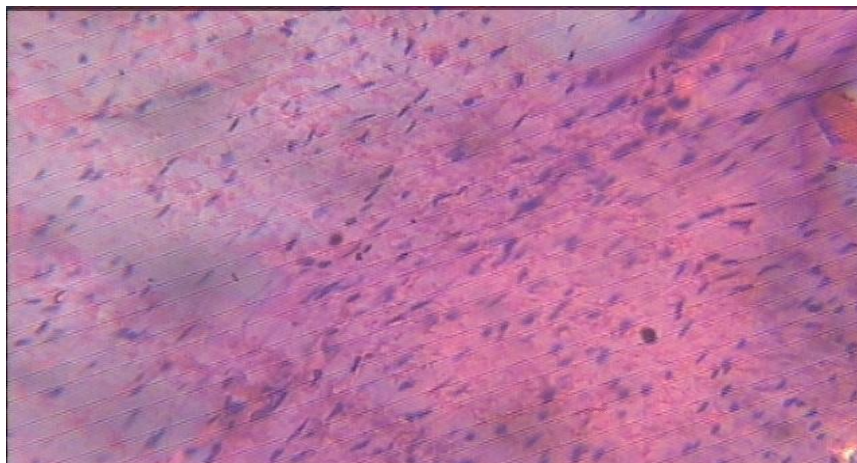
**Fig. 9. Photomicrograph of the section of the spleen in the control group which shows lymphocytic infiltrates particularly at the splenic pulp. Other features are normal. Mag. X 100(H&E)**



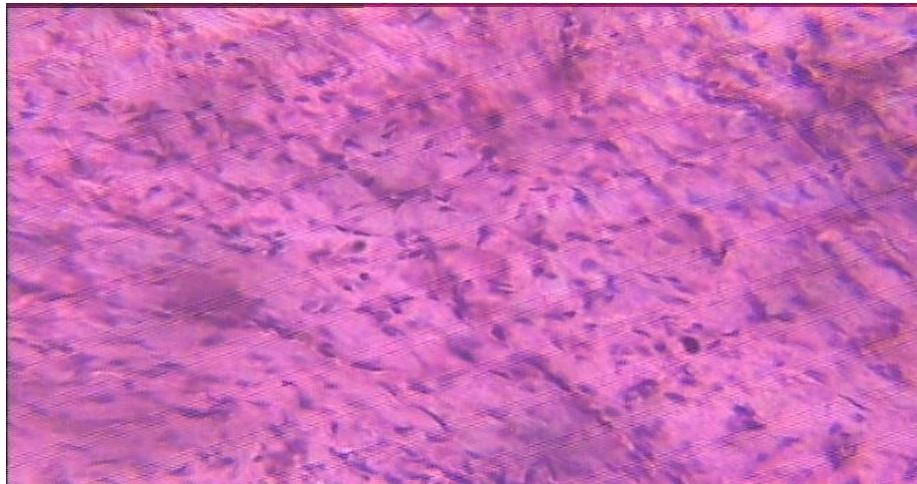
**Fig. 10. Photomicrograph of the section of the spleen of rat fed with 1000mg/kg of MSG which reveals the generalized fatty change. Surviving areas have massive inflammatory infiltrates and hypertrophy. There are also edematous degenerative changes at the medulla and pulp. Mag. X 100 (H&E)**



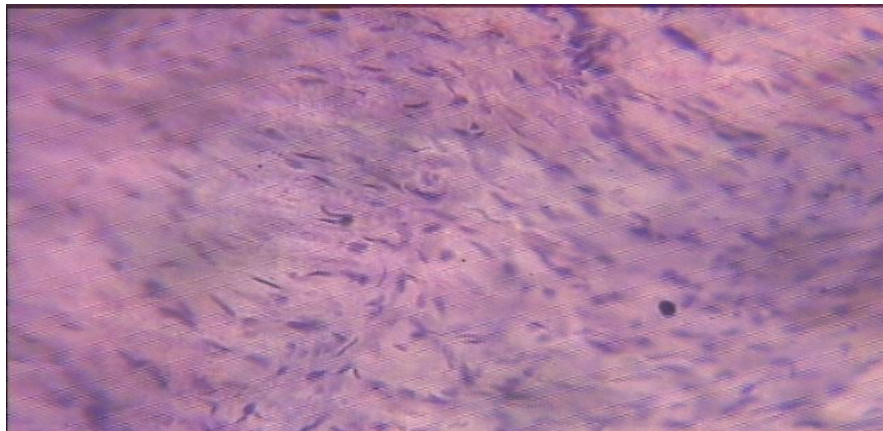
**Fig. 11. Photomicrograph of the section of the spleen of rat fed with 1250 mg/kg of MSG, which shows loss of splenic tissue architecture and massive infiltration of inflammatory cells. Even though vascular presence is visible, they remain as a mark of ghost feature. Mag. X 100 (H&E)**



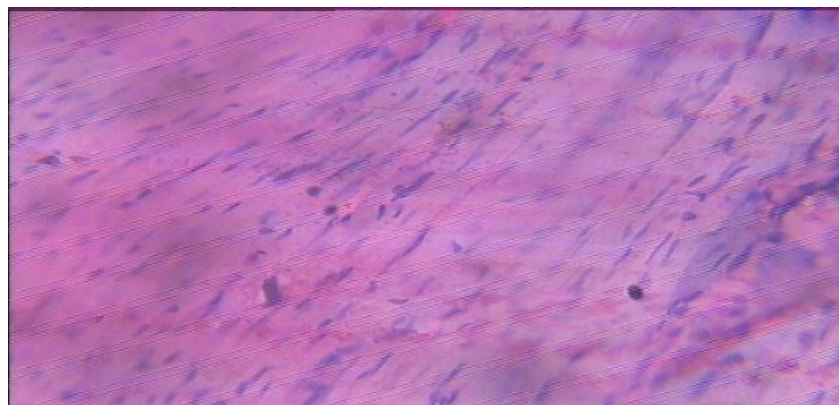
**Fig. 12. Photomicrograph of the section of the heart in the control group reveals normal cardiac myocytes. Mag. X 100(H&E)**



**Fig. 13. Photomicrograph of the section of the heart of the rat fed with 500 mg/kg of MSG, shows necrosis of the heart muscles with apparent inflammatory infiltrates. There are obvious pavementation and hypertrophy of the cardiac valves. Mag. X 100(H&E)**

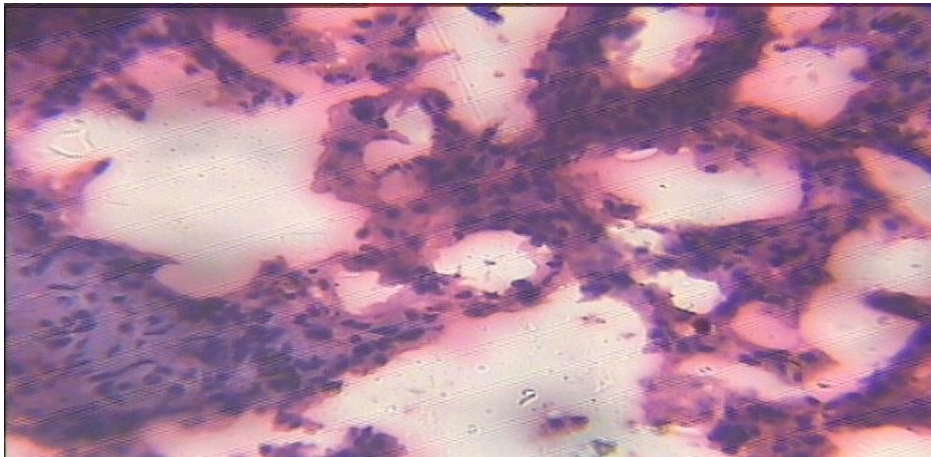


**Fig. 14. Photomicrograph of the section of the heart of rat fed with 750mg/kg of MSG. Here there is pronounced necrosis. Vascular supply is hardly observed and haemorrhage is pronounced in all the heart muscles. Inflammatory cells infiltrate accompany edematous changes at the valves. Mag. X 100(H&E)**

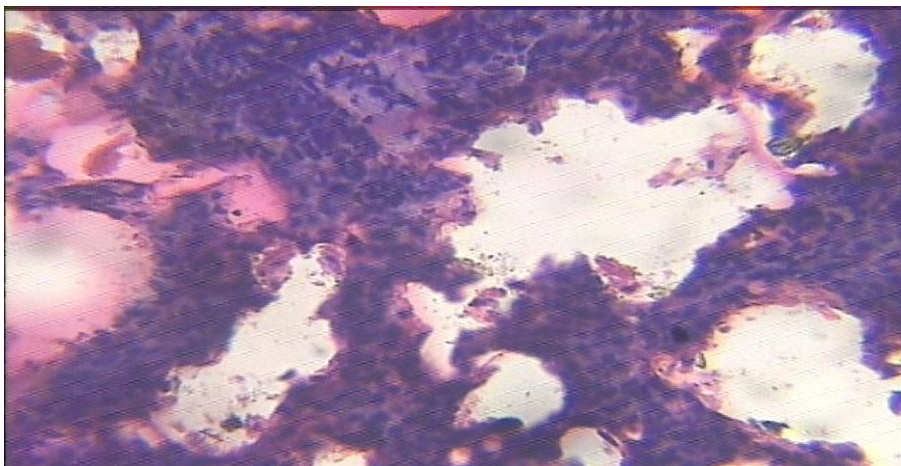


**Fig. 15. Photomicrograph of the section of the heart of rat fed with 1250 mg/kg of MSG showed degenerative changes of heart muscle cells, with nuclear clumping and dissolution in some places. Mag. X 100(H&E)**

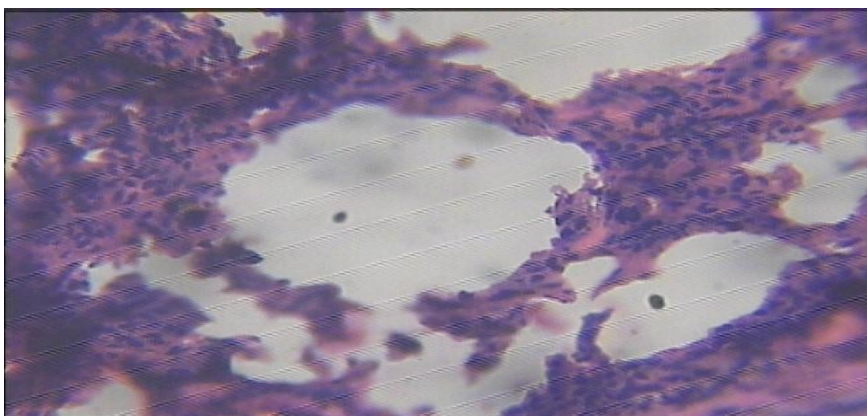




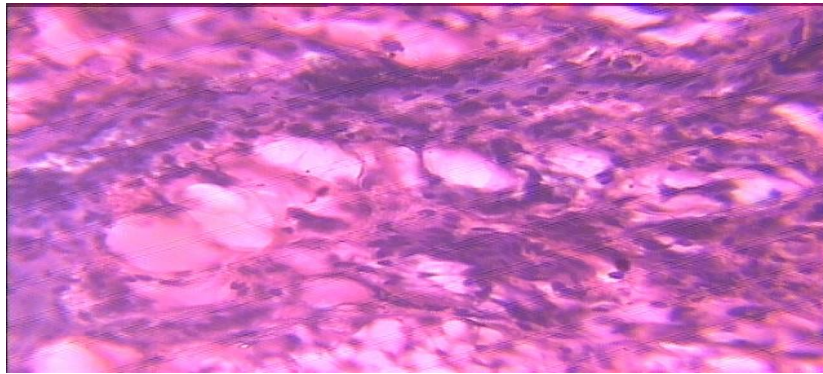
**Fig. 16.** Photomicrograph of the section of the lungs in the control group. Mag. X 100(H&E)



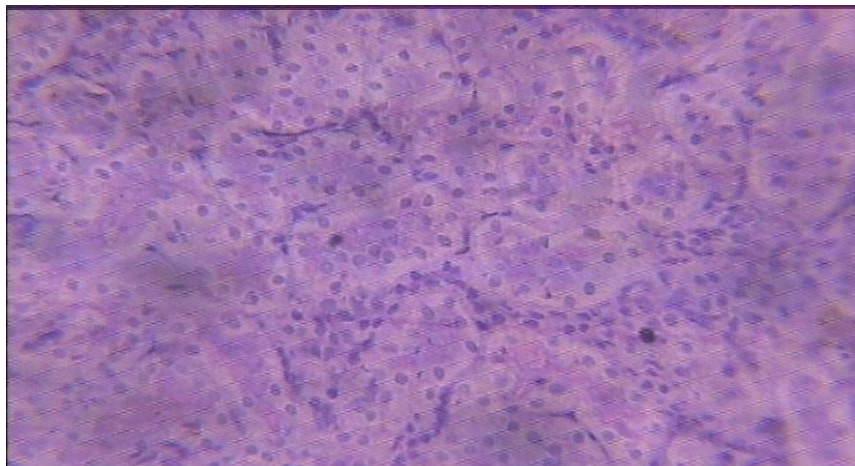
**Fig. 17.** Photomicrograph of the section of the lungs of rat fed with 750 mg/kg of MSG, which shows massive necrosis, with surviving alveolar of various shapes and sizes. There are edematous terminal bronchioles and adjacent cells necrosis, with hypertrophy of the alveolar septa. Mag. X 100(H&E)



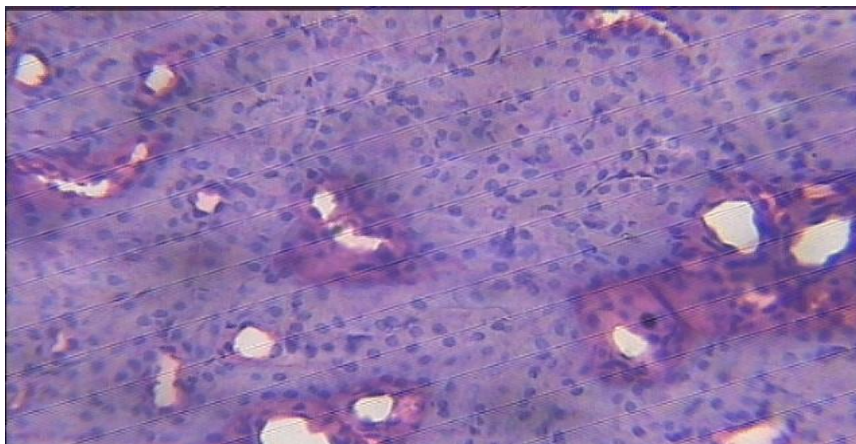
**Fig. 18.** Photomicrograph of the section of lung of rat fed with 1250mg/kg of MSG. Here, there is a dissolution of lung tissue due to cell death. Bronchioles and alveolar spaces cannot be recognized. Alveolar septa are disintegrated leaving, an irregular features of necrotized vessels. Mag. X 100(H&E)



**Fig. 19. Photomicrograph of the section of the kidney in the control group, which showed normal histological features. The section indicated detailed cortical parenchyma and the renal corpuscles appeared as dense rounded structures with the glomerulus surrounded by a narrow Bowman's spaces. Mag.X100(H&E)**



**Fig. 20. Photomicrograph of the section of the kidney of the rat fed with 750mg/kg of MSG, which showed massive renal tissue loss with hypertrophy of the calyces. Surviving glomeruli are left without Bowman's capsule; fibrosis is minimal at the cortical area. Mag. X 100(H&E)**



**Fig. 21. Photomicrograph of the section of the kidney of rat fed with 1250mg/kg of MSG, which showed no feature representative of renal tissue. Rather irregular spaces of various shapes and sizes are observable. There are inflammatory cell infiltrates whose nuclear picture is that of the necrosed cell. Mag. X 100(H&E)**

### **3.6 Effects of MSG on the Histological Sections of the Heart**

Animals fed with MSG showed necrosis of the heart muscles with apparent inflammatory infiltrates. There were obvious pavement-tion and hypertrophy of the cardiac valves. Vascular supply was hardly observed and haemorrhage was pronounced in all the heart muscles.

### **3.7 Effects of MSG on the Histological Section of the Lungs**

Feeding of animals with MSG treated-diet led to dissolution of lung tissue due to cell death. Bronchioles and alveolar spaces were not recognized. Alveolar septa were disintegrated leaving, an irregular features of necrotized vessels.

### **3.8 Effects of MSG on the Histological Section of the Kidney**

Feeding of animals with MSG treated-diet resulted in massive renal tissue loss with hypertrophy of the calyces. Surviving glomeruli were left without Bowman's capsule; fibrosis was minimal at the cortical area.

## **4. DISCUSSION**

The results of the haematoxylin and eosin staining (H & E) of the testes showed cystic degenerative changes with some intracellular vacuolations and patchy areas of necrosis, appearing in the stroma of the seminiferous tubules of the group fed with 1000 mg/kg body weight of MSG, when compared with those of the control group. This toxic effect on the testes observed in this experiment agrees with the possible effects already reported by Onakewhor et al. [17] and Moses et al. [18]. The actual mechanism by which it induces cellular degenerative and atrophic changes is unclear. However, degenerative changes have been reported to result in cell death, which is of two types namely apoptotic and necrotic cell death. These two types differ morphologically and biochemically [19].

Pathological or accidental cell death is regarded as necrotic and could result from extrinsic insults to the cell such as osmotic, thermal, toxic and traumatic effects [20]. MSG could have acted as toxins to the cells of the testes. The process of cellular necrosis involves the disruption of the membrane's structural and functional integrity. In cellular necrosis, the rate of progression depends on the severity of environmental insults [21].

In the liver, an increase in the consumption of MSG treated-diet, resulted in massive necrosis in the hepatocytes and distortion of its cytoarchitecture in the treatment groups when compared with those of the control group. The necrosis observed in the liver might follow the same mechanism of necrosis observed by Eweka and Om'Iniaboh's [22] who reported that MSG had a destructive effect on Brunner's gland of the duodenum and the small intestinal mucosa of adult Wistar rat. The result of this study suggests that the distortion of the liver architecture could be associated with functional changes that may be detrimental to health. The proliferating cells of the liver which produce red and white blood cells are normally found between the hepatic cells and walls of the vessels [23]. As a result of the distortion and dilatation of the hepatocytes and their central vein, the haemopoietic function of the liver may have been highly affected as a result of possible toxic effect of MSG cellular degeneration which has been reported to result in cell death, which occurs as a controlled event involving a genetic programme in which caspase enzymes are activated [24]. Ischemic or pharmacologic disruption of cellular transporters can cause swelling of the parenchyma of the liver cells.

The disruption caused by MSG is a cardinal feature of the results of this study. Though there are many different causes of cell swelling including drug poisoning, water intoxication, hypoxia from asphyxia and acute hyponatremia [25]. MSG may have acted as toxins to the hepatocytes, affecting their cellular integrity and causing a defect in membrane permeability and cell volume homeostasis. The cellular hypertrophy observed may have been caused by the cytotoxic effect of normal detoxification processes and other functions of the liver.

In the spleen of the respective treated groups, there were generalized fatty change, tissue hypertrophy and massive infiltration of inflammatory cells. There were also edematous degenerative changes at the medulla and pulps. Even though vascular presences are visible, they remain as a mark of ghost feature. Histological features in the control group were normal. The fatty change reported in this study may have been induced by the toxic level of monosodium glutamate. This can also be seen in the liver, muscle and kidney. Other causes of fatty change (steatosis) include protein malnutrition, diabetes mellitus, obesity, and anoxia. In industrialized nations, alcohol abuse is so far the most

common cause of fatty change especially in the liver [26].

In the heart, there was necrosis of the cardiac muscles, obvious pavementation, hypertrophy and edematous changes at the cardiac valves. There were also degenerative changes in muscle cells, with nuclear clumping and dissolution in some places. The control group reveals normal cardiac myocytes.

In the lungs of animals treated with 1,250 mg/kg body weight MSG, there was massive necrosis, edematous changes at the terminal bronchioles, and hypertrophy of the alveolar septa. The control section shows dense mononuclear infiltrate particularly at the alveolar spaces.

In the kidney, there were varying degrees of cytoarchitectural distortion and reduction in the number of renal corpuscles in all the treated groups which were at variance with the control respectively. There were degenerative and atrophic changes with inflammatory infiltrates observed in the group that received the highest dose of MSG. It may be inferred from the present study that prolonged administration of high dose monosodium glutamate resulted in degenerative and atrophic changes observed in the renal corpuscles.

The actual mechanism by which monosodium glutamate-induced cellular degeneration observed in this study needs further investigation. The necrosis observed is probably due to the high concentration of the MSG on the kidney. Pathological or accidental cell death is regarded as necrotic and could result from extrinsic insults to the cell as osmotic, thermal, toxic and traumatic effects [20].

The process of cellular necrosis involves disruption of membranes, as well as structural and functional integrity. Cellular necrosis is not induced by stimuli intrinsic to the cells as in programmed cell death (PCD), but by an abrupt environmental perturbation and departure from the normal physiological conditions [27].

## 5. CONCLUSION

The present study suggests that prolonged administration of MSG at high doses resulted in an increased toxic effect on many organs in the body. MSG affects these organs negatively by decreasing their sizes, activity and functions. Thus, caution should be taken in its use as a flavour enhancer at home and industries.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

Animal ethic Committee approval has been collected and preserved by the author.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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