

Organ toxicity of monosodium glutamate in adult albino Wistar rats

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Abstract

Objectives: To determine the LD50 and organ toxicity of monosodium glutamate (MSG). **Materials and Methods:** A total of 30 adult albino Wistar rats of both sexes were used in this study. Fifteen of them were used for acute toxicity test. The second stage of the experiment was performed with 15 rats which received 500 mg/kg, 750 mg/kg, 1000 mg/kg, and 1250 mg/kg of MSG thoroughly mixed with the feeds, respectively, with unlimited supply of drinking water on daily basis for 8 weeks. Group E, which was the control, received an equal amount of feeds without MSG. The animals' weights were measured weekly, constantly observed daily for systemic effects and later sacrificed at the end of 8 weeks in a desiccator under anesthesia with ether following an overnight fast. Blood was obtained by left ventricular cardiac puncture for biochemical analysis. The kidneys, heart, lungs, spleen, liver, and testis were dissected and fixed in 10% formal saline for histological examination using hematoxylin and eosin (Hand E) methods. **Results:** There was a significant increase in the mean weight of the animals and controls ($P < 0.05$). There was a significant decrease in the mean serum cholesterol levels, a significant increase in the mean fasting plasma glucose, and plasma alanine transferase levels of the experimental animals when compared with the controls ($P < 0.05$). The histological finding revealed a reduction in spermatocytes in testes of animals fed with 1000 mg/kg MSG plus necrosis and scanty seminiferous tubules. There was massive necrosis on the liver and lungs, fatty change in the spleen and degenerative changes of heart muscle cells. There were also irregular spaces of various shapes and sizes and necrosis in the kidney. **Conclusion:** The study demonstrated that consumption of MSG has deleterious effects in virtually all organs which will apparently affect their functions.

Key words: Albino rats, monosodium glutamate, organ, toxicity

INTRODUCTION

Noxious substances abound in our environment. We come in contact with them every day, either directly or indirectly. In either way, they may have an effect on our organs

in particular and health in general. Few of these noxious substances such as carbon monoxide are inhaled; some such as are alcohol and tobacco are consumed, and much of these substances are added to our food in the form of additives. Most food additives act either as preservatives or enhancers of palatability. One of such food additive is monosodium glutamate (MSG). It is sold in most open markets and stores in Nigeria as "Ajinomoto," marketed by West African Seasoning Company Limited, as "Vedan" or "white magi" marketed by Mac and Mei (Nig) Limited.

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The flavor-enhancing power of MSG was discovered to be glutamate by Dr. Kikunae Ikeda in 1908.^[1] Glutamate is one of the most commonly occurring amino acids. It plays a crucial role in a broad variety of metabolic process, such as in the detoxification of drugs.^[2] It is also responsible for 75% of the excitatory neurotransmission in the brain.^[3] MSG is readily utilized by glutamate receptors throughout the mammalian body. These receptors could be found in the brain, spinal cord, conducting system; nerve terminals, kidney, liver, testis, lungs, spleen, and heart. Therefore, advocates of food safety should consider these organs as potential sites of damage.^[4] Neural injury associated with trauma, stroke, epilepsy, and many neurodegenerative diseases such as Alzheimer's, Huntington's, Parkinson's disease, and Amyotrophic lateral sclerosis was reported to have been mediated by excessive activation of the glutamate receptors.^[5] Thus, the free glutamic acid can get into the brain injuring and frequently killing neurons.^[6]

Adverse systemic reactions associated with consumption of MSG include: Arrhythmias, hypertension, angina, myalgia, arthritis, depression, dizziness, anxiety, hyperactivity, insomnia, numbness, seizures, diarrhea, nausea and vomiting, shortness of breath, nocturia, oligozoospermia.^[7]

Food containing MSG can be identified in the market with the following names: Enzyme modified, anything protein fortified or fermented, autolyzed yeast, broth, bouillon, natural flavoring, gelatin, olyzed protein, pectin, soy protein, sauce, stock, whey protein, yeast extract, and yeast food.^[8]

MSG has been used in newborn laboratory mice to induce adult obesity.^[9] This is because of the lesion it provokes in the arcuate nucleus of the hypothalamus, resulting in increased caloric intake above utilization of calories.^[3] MSG has been shown to trigger epileptic convulsions in rats. The severity of the convulsions and death incidence increased progressively with age.^[10]

MSG has a toxic effect on the testis by causing significant oligozoospermia and increased abnormal sperm morphology in a dose-dependent fashion in adult male Wistar rats.^[11] It has been implicated in male infertility, by causing testicular hemorrhage, degeneration, and alteration of sperm cell population and morphology.^[12]

It has been reported that MSG has neurotoxic effects resulting in brain damage,^[13] retinal degeneration, endocrine disorder, and some pathological conditions such as addiction, stroke, epilepsy, brain trauma, neuropathic pain, schizophrenia, anxiety, Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis.^[14]

MATERIALS AND METHODS

Thirty adult Wistar rats of both sexes with average weight 160–200g were used for the study. Fifteen rats were used for acute toxicity test and the remaining 15 for the second stage of the experiment.

They were each assigned into five groups: Treatment group A, B, C, and D of $n = 12$ and control group of $n = 3$. The animals were obtained and bred at uniform conditions in the animal house of the Department of Pharmacology, College of Medicine, Abia State University, Uturu, Nigeria. They were acclimatized for 7 days before the study. The animals had free access to standard animal feeds purchased from a local commercial supplier and water *ad libitum* and housed under standard conditions of temperature ($25^{\circ}\text{C} \pm 20^{\circ}\text{C}$), under 12 h light-darkness cycles. The MSG (3 g/satchet containing 99% MSG) was obtained from a grocery store at New Market, Aba in Abia State.

Monosodium glutamate administration

The rats in the treatment group A, B, C, and D were given, respectively, 500 mg/kg, 750 mg/kg, 1000 mg/kg, and 1250 mg/kg of MSG thoroughly mixed with their feeds, respectively, on a daily basis for 8 weeks. The control group E received equal amounts of feeds without MSG. The animals were sacrificed at the end of 8 weeks under anesthesia with ether after an overnight fast. About 3 ml of blood was obtained by left ventricular cardiac puncture from the rat and placed in a container for biochemical analysis. The kidneys, heart, lungs, spleen, liver, and testis were quickly dissected and fixed in 10% formal saline for routine histological technique.

Histological study

The tissues were dehydrated in ascending grade of alcohol (ethanol), cleared in xylene and embedded in paraffin wax. Serial sections of 6 microns thick were obtained using a rotatory microtome. The deparaffinized sections were stained routinely with hematoxyline and eosin (H and E). Photomicrographs of the desired sections were made for further observations.

Blood collected from the rats was used for fasting plasma glucose, cholesterol, and serum Alanine transaminase (ALT) estimation. Plasma glucose was assayed by Trinder (oxidase-peroxidase system).^[15] The serum cholesterol was determined by the method of enzymatic hydrolysis and oxidation.^[15] The serum ALT activity was assayed by a method of Reitman and Frankel.^[16] All determinations were performed within 24 h of a collection of sample.

Data were analyzed for mean, standard deviation, and compared for significance between the control and experimental groups using Chi-square. The level of significance for all experiment was $P < 0.05$.

RESULTS

The median lethal dose LD50 was found to be 500 mg/kg. This is the median of 200 mg/kg which did not kill any of the animals so administered and 800 mg/kg that killed all its animals.

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 1250 mg/kg of MSG developed bulging of eyeballs (exophthalmos), blurred

vision, and had several bouts of seizures before its demise six days later. Most of the animals gained maximal weight in the course of the study.

Table 1 presents the weights of the experimental animals and the control. There was a significant increase in the mean weights of the treated animals when compared to their control, as well as among the different groups ($P < 0.05$).

Tables 2-4 show the mean serum cholesterol, glucose, and plasma ALT levels between the experimental and control. There was a significant decrease in the mean serum cholesterol and increase in the mean fasting plasma glucose and ALT levels of experimental animals compared to their controls ($P < 0.05$).

The testes of the animals in the control group showed normal testicular cells with dilatation of ducts [Figure 1]. The treatment section with 1000 mg/kg of MSG after 8 weeks

revealed a reduction in spermatocytes, vacuolation, a patchy area of necrosis, and scanty seminiferous tubules [Figure 2].

The rats in the control group showed infiltrates of normal hepatocytes in the liver [Figure 3]. The rats in the treatment group fed with 1000 mg/kg of MSG showed massive necrosis of the liver [Figure 4]. The spleen (control section) showed normal features with lymphocytic infiltrates particularly at the splenic pulp [Figure 5]. Group treated with 1000 mg/kg of MSG showed fatty change [Figure 6].

The control group's hearts had normal cardiac myocytes [Figure 7]. The section treated with 1250 mg/kg of MSG revealed degenerative changes of heart muscle cells and necrosis [Figure 8].

The control group's lungs showed dense mononuclear infiltrates particularly at the alveolar spaces [Figure 9]. The group treated with 1250 mg/kg of MSG revealed necrosis and dissolution of lung tissue due to cell death [Figure 10].

The control section of the kidney showed normal histological features with detailed cortical parenchyma [Figure 11]. The section treated with 1250 mg/kg MSG showed necrosis and irregular spaces of various shapes and sizes [Figure 12].

DISCUSSION

Consumption of MSG worldwide with its attendant toxic effects still remains a concern to medical and food scientists.

Table 1: Mean weekly weights of adult Wistar rat treated with different doses of MSG

Weeks	Mean weight (g) dose (mg/kg)				
	Control	500	750	1000	1250
1	172	158	165	188	185
2	183	195	201	220	210
3	185.6	195	206	220	212
4	189.7	222	225	215	226
5	190.3	193	210	215	223
6	191.3	216	222	222	228
7	190.3	215	182	198	217
8	193	195	208	197	210

MSG - Monosodium glutamate

Table 2: Mean values of serum cholesterol levels for experimental animals and control after 8 weeks

	Control	A 500 mg/kg	B 750 mg/kg	C 1000 mg/kg	D 1250 mg/kg
Mean serum cholesterol (mg/dl)±SEM	65.5±3.5	51.5±10.5	51.5±0.5	57.0±5.0	51.0±0.0
χ^2	3.84	3.81	0.11	1.22	0.15
df	1	1	1	1	1
Number of rats	3	3	3	3	3
Probability	$P < 0.05$				

SEM - Standard error of mean, χ^2 - Chi-square, df - Degrees of freedom

Table 3: Mean values of FPG for experimental animals and control after 8 weeks

	Control	A 500 mg/kg	B 750 mg/kg	C 1000 mg/kg	D 1250 mg/kg
Mean FPG (mg/dl)±SEM	63.0±7.0	61.0±17.0	96.0±4.0	82.5±11.5	83.0±12.0
χ^2	3.84	1.81	0.37	4.48	4.70
df	1	1	1	1	1
Number of rats	3	3	3	3	3
Probability	$P < 0.05$				

SEM - Standard error of mean, χ^2 - Chi-square, df - Degrees of freedom, FPG - Fasting plasma glucose

Table 4: Mean values of plasma ALT levels for experimental animals and control after 8 weeks

	Control	A 500 mg/kg	B 750 mg/kg	C 1000 mg/kg	D 1250 mg/kg
Mean ALT (IU/L)±SEM	19.0±2.5	35.0±10.0	34.0±9.0	33.5±9.5	33.5±10.5
χ^2	3.84	3.37	3.88	4.25	4.92
df	1	1	1	1	1
Number of rats	3	3	3	3	3
Probability	$P < 0.05$				

SEM - Standard error of mean, χ^2 - Chi-square, df - Degrees of freedom, ALT - Alanine transaminase

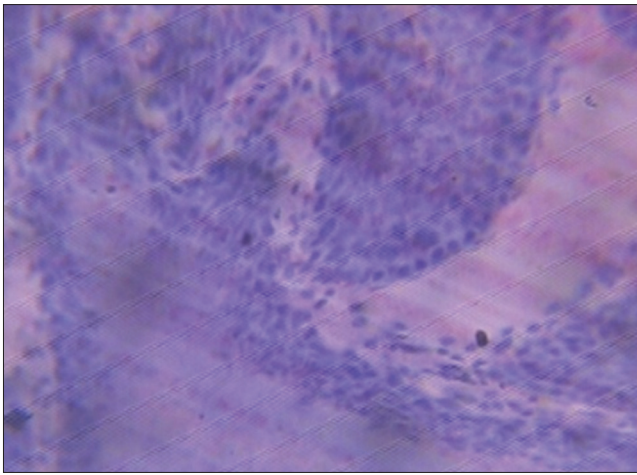


Figure 1: Testis (control section)

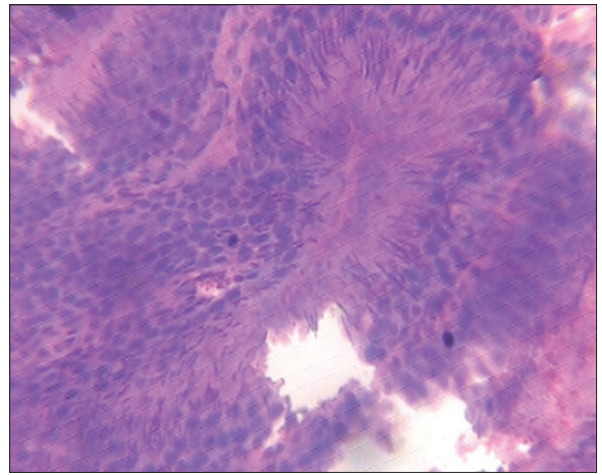


Figure 2: Testis (1000 mg/kg of monosodium glutamate)

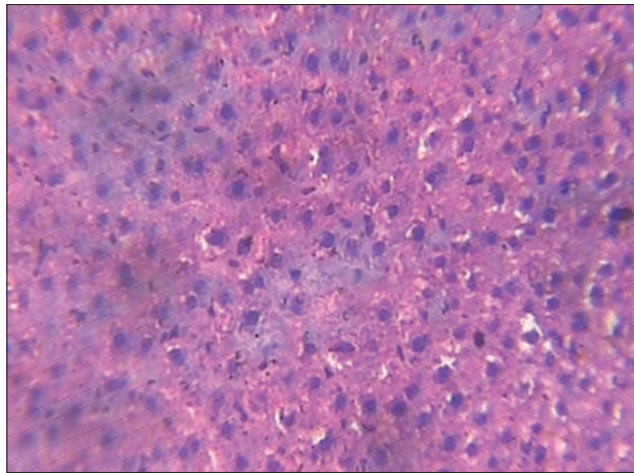


Figure 3: Liver (control group)

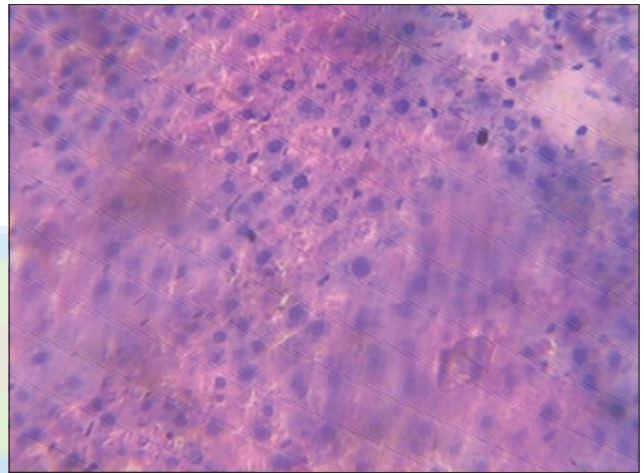


Figure 4: Liver (1000 mg/kg of monosodium glutamate)

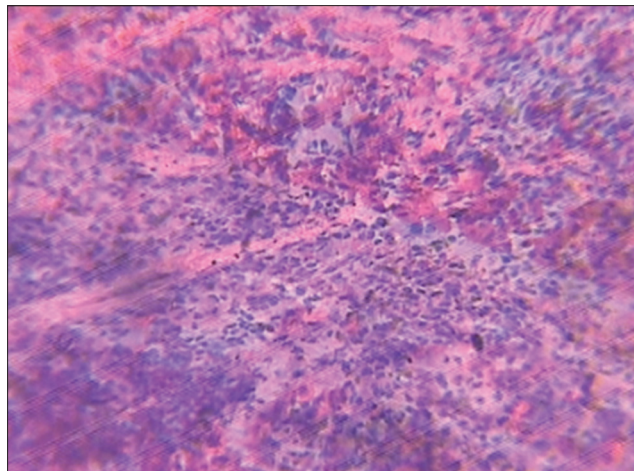


Figure 5: Spleen (control group)

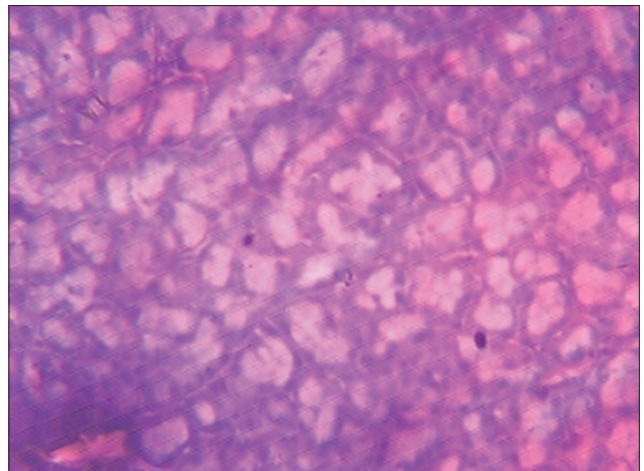


Figure 6: Spleen (1000 mg/kg of monosodium glutamate)

A significant increase in weight was observed in rats fed with MSG. This was comparable to a similar study carried out to induce obesity in laboratory mice.^[9] This is probably because of the effect that it provokes in the arcuate nucleus of the hypothalamus, resulting in increased caloric intake above

utilization.^[3] MSG also increases appetite and improves the palatability of the poor quality diet.^[17] There was a significant decrease in the mean cholesterol compared with the control. This is in contrast with the work of Savastanon *et al.* where the cholesterol level of the experimental group was higher

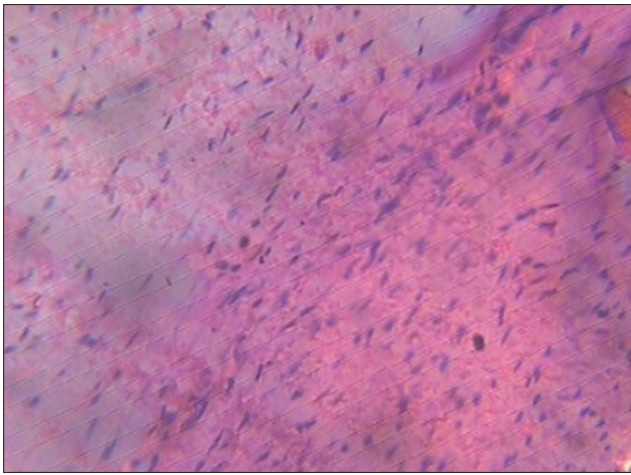


Figure 7: Heart (control group)

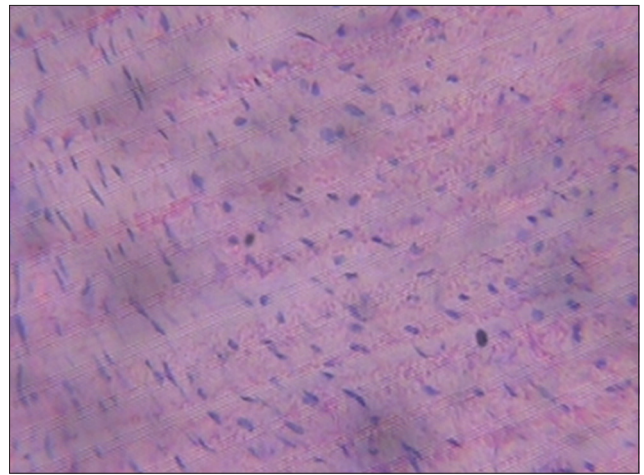


Figure 8: Heart (1250 mg/kg of monosodium glutamate)

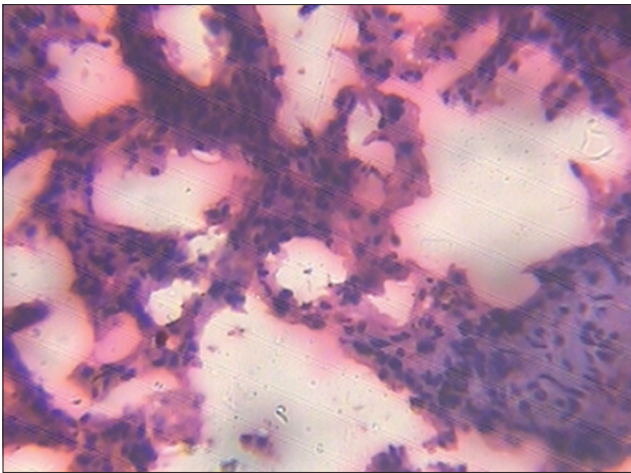


Figure 9: Lungs (control group)

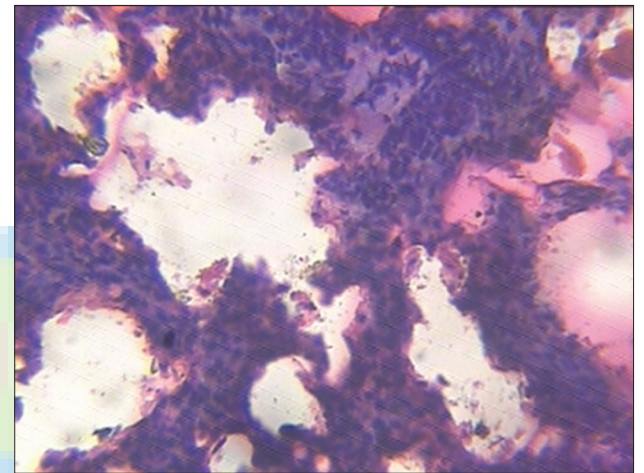


Figure 10: Lungs (1250 mg/kg of monosodium glutamate)

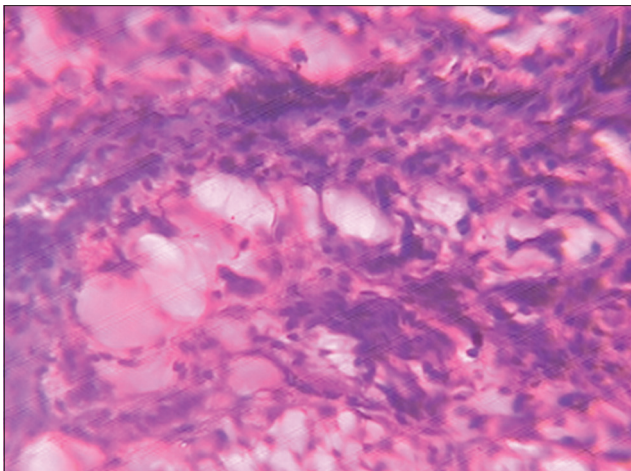


Figure 11: Kidney (control group)

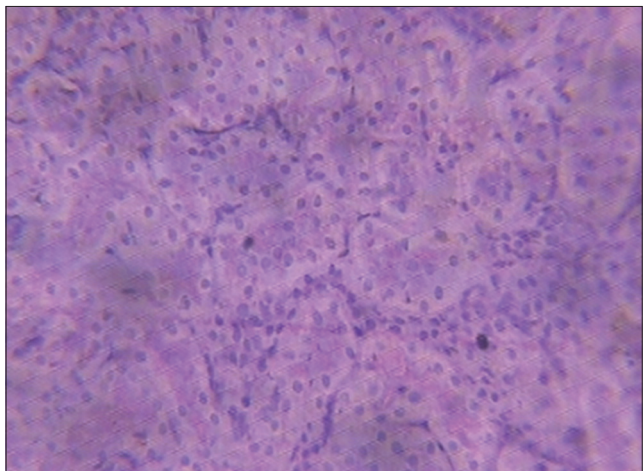


Figure 12: Kidney (1250 mg/kg of monosodium glutamate)

than control.^[18] This could be attributed to the activation of the enzyme, 3-hydroxy-3-methoxyglutamyl-CoA reductase, which catalyzed the rate-limiting step of cholesterol synthesis.

Concerning glucose level, a significant increase was

observed in the treated group compared to the controls. This result compares favorably with the work of Negata *et al.*, where MSG was used to induce obesity in type 2 (noninsulin-dependent) diabetes mellitus in mice due to elevated blood glucose.^[19]

A significant increase in the serum ALT was observed in the MSG-treated rats compared to the control [Table 4].

This study was necessitated by the observed indiscriminate use of MSG in Nigeria for seasoning and flavor enhancing purposes without taking into consideration the possible adverse effects from its use over time, even at low concentrations. The ALT enzyme is a sensitive marker of liver damage.^[20] Therefore, the increase in serum ALT activity by 1%, 10.7%, and 28.1% in rats fed with MSG of 750 mg/kg, 1000 mg/kg, and 1250 mg/kg respectively, may perhaps be an indication of liver damage.

Thus MSG may be hepatotoxic at 750 mg/kg and above, hence should be avoided during the treatment of liver disorders. Since ALT was found to be a positive indicator of insulin resistance, diabetes mellitus and obesity,^[21] which are risk factors for coronary disease,^[22] the use of MSG at even low dose should not be encouraged because of the possible untoward implications.

The results of the H and E staining of the testis showed reduction in spermatocytes, vacuolations, patchy areas of necrosis and scanty seminiferous tubules of the group treated with 1000 mg/kg of MSG compared to the control. The vacuolations observed may be due to MSG interference.^[11]

In the liver, with increasing dose of MSG there was massive necrosis in the central vein and distortion of its cytoarchitecture compared to the control section. This distortion could be associated with functional changes that may be detrimental to health and may affect the hemopoietic function of the liver resulting in cell death. This occurs as a controlled event involving a genetic program in which caspase enzymes are activated.^[23]

In the spleens of the treated group, there was generalized fatty change, tissue hypertrophy, and massive infiltration of inflammatory cells. Histological features in the control group were normal. The fatty change reported in this study may have been induced by the toxic level of MSG. 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.^[24]

In the heart, there were degenerative changes of the cardiac muscles and necrosis. The mechanism by which MSG does this needs further investigation.

In the kidney, there was necrosis, reduction in the number of renal corpuscles and irregular shapes of various sizes in the treated group which was at variance with the control.

The necrosis observed may have been due to high doses of MSG on the kidney. Pathological or accidental death is regarded as necrotic and could result from extrinsic insults to the cell as osmotic, thermal, toxic, and traumatic effects.^[25]

CONCLUSION

Our study demonstrates that consumption of MSG has deleterious effects on virtually all the organs which will apparently affect their functions. Such negative effects call for caution in its use as a flavor enhancer and in industries.

It is, therefore, recommended that further studies be carried out to establish the mechanism by which effects its deleterious effects in the body.

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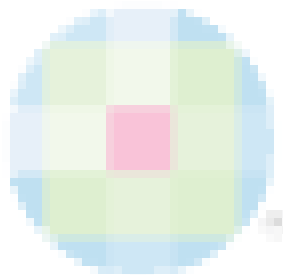
Conflicts of interest

There are no conflicts of interest.

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