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HISTOLOGICAL EFFECT OF HIGH-DOSES OF MONOSODIUM GLUTAMATE ON THE LIVER OF ADULT WISTAR RAT

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ABSTRACT

This study determined the high-dosage effect of oral administration of Monosodium Glutamate (MSG) on body weight and liver histology using 25 adult Wistar rats of both sexes and weighing between 140g – 160g (±22.36g). The rats were subdivided into five groups (A, B, C, D and E; n=5 each) and allowed to acclimatize for 2 weeks with free access to feed and water *ad libitum*. After acclimatization, test groups (B - E) received graded doses of MSG in the following order: 20mg, 40mg, 80mg, 120mg and 160mg/day for 4 weeks respectively. The weights of the Wistar rats before and after acclimatization, and after each week of administration of MSG, were appropriately recorded. At the end of the 4-week MSG administration, the liver tissues of the rats were harvested for histology using routine methods. The results showed that test group B liver sections presented no changes in liver architecture as compared to the control group. However, test group C presented vacuolations, while D and E presented degenerative changes in the form of interstitial, sinusoidal congestion and increased basophilia; suggesting that excessive consumption of MSG over time, will adversely affect the liver, while showing no relationship between MSG and weight gain.

Key words: Monosodium, Glutamate, Wistar rats, Liver, Consumption

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INTRODUCTION

In order to enjoy food, taste and flavor are necessary. A tasteless food even when composed of required nutritional elements is usually rejected. Therefore, food flavoring is important especially in elderly persons who have irreversible chemosensory deficit. In such individuals it is necessary to improve appetite to ensure adequate dietary intake. Flavor enhancers are also useful in situations where salt intake needs to be reduced such as in hypertension. Glutamate possesses umami taste which enhances food palatability and encourages flavor acceptance (Fuke and Shimizu, 1993).

Glutamateis one of the non-essential amino acids that are synthesized endogenously. It is a component of many proteins and peptides. When bound to protein, glutamate is tasteless. The sweet umami taste and flavor becomes perceptible only when free glutamate dissociates from proteins during the processes of fermentation, ripening and cooking. Tomatoes, cheese and mushrooms contain large quantity of glutamate and are thus used to enrich the taste and flavor of food (Giacometti *et al.,* 1979). However, it is believed that the use of excess amount of glutamate could be harmful to man (Kurihara, 2009), hence the need to carry out this study to determine its actual effect on the liver using animal models.

This flavor enhancer is extensively used in the food industry, and in restaurants and homes. It is present in a wide variety of processed foods including flavored chips and snacks, soups or sauces (canned, packed), prepared meals, frozen foods, marinated meats, fresh sausages, bottled soy or oriental sauces, and stuffed or seasoned chicken, manufactured meats, some hams, luncheon chicken and turkey, flavored tuna, vegetarian

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burgers and sausages (Giacometti *et al.,* 1979). Glutamate occurs naturally in various foods including cheeses, seafood, meat broths, poultry and vegetables. Although there is no problem if MSG is present in small amounts in any food, the problem moves to a much graver scale if small amounts are in different common foods that are consumed daily. Moreover, MSG might fall under different titles, making it very difficult to determine what foods contain this additive (Raben *et al.,* 2003). The Food and Drug Administration (FDA) the united states categorized MSG as a safe substance in 1959.However, the FDA commissioned a report that an unknown percentage of the population might react to MSG and develop MSG symptom complex (FDA, 2004).

An experimental study has shown that prolonged consumption of MSG produced a myriad of toxic effects referred to as Chinese restaurant syndrome (Raiten *et al.,* 1996). This syndrome was characterized by sweating, nausea, headache, chest tightness, and/or a burning sensation in the back of the neck. Furthermore, long-term intake of MSG was shown to induce hyperphagia, obesity, asthma, memory impairment, and damage to hypothalamic neurons. Thus, the addition of MSG to foods can ultimately be considered a health hazard (Taliaferro, 1995).

The liver is a reddish-brown wedge-shaped organ with four lobes of unequal size and shape. A human liver normally weighs 1.44–1.66 kg (3.2–3.7 lb) and has a width of about 15 cm. It is both the heaviest internal organ and the largest gland in the human body. Located in the right upper quadrant of the abdominal cavity, it rests just below the diaphragm, to the right of the stomach and overlies the gallbladder (Cotran *et al.,* 2005).

The liver has a wide range of functions, including detoxification of various metabolites, protein synthesis, and the production of biochemicals necessary for digestion (Abdel-Misih and Bloomston, 2010).

Because of its strategic location and multidimensional functions, the liver is also prone to many diseases. Hepatic encephalopathy is caused by an accumulation of toxins in the bloodstream that are normally removed by the liver. This condition can result in coma and can prove fatal. Other disorders caused by excessive alcohol consumption are grouped under alcoholic liver diseases and these include alcoholic hepatitis, fatty liver, and cirrhosis. Factors contributing to the development of alcoholic liver diseases are not only the quantity and frequency of alcohol consumption, but can also include gender, genetics, and liver insult (Saxena and Theise, 2004). Liver damage can also be caused by drugs such as paracetamol, drugs used to treat cancer and toxins including toxins in food additives. The liver play a major role in metabolism including regulation of glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production, and detoxification (Abdel-Misih and Bloomston, 2010).

MATERIALS AND METHODS

Research Design: A total of twenty-five rats of comparable sizes were used for the study. The experimental animals were divided into five groups (A-E) housed using five big cages elevated from the ground to prevent them from getting infection. Group A served as the control and the rats were given distilled water and normal feed (grower's mash) with no administration of the monosodium glutamate. Group B, C, D and E received graded doses of the monosodium glutamate (40mg, 80mg, 120mg and 160mg) prepared carefully (alongside normal feed - grower's mash) and administered for a period of 28days. ANOVA was used to analyse the results of the weight and differences was considered significant at $P<0.05$ level of confidence. All data was expressed as Mean ± Standard deviation. This experimental study was carried out at the Histology and Histopathology Laboratories of the College of Medical Sciences, Ambrose Alli University Ekpoma, Edo State, Nigeria.

Experimental Animal/ Housing Condition: Twenty-five adult Wistar rats of both sexes of comparable sizes and weights ranging from 100-200grams were procured from the animal house of Basic Medical Science College of Medicine. The rats were acclimatized for two weeks (14days), kept in wire mesh cages elevated from the ground and the animal beds were changed weekly with fresh saw dust. During the acclimatization period, the rats were fed with grower's marsh and water ad libitum. The house was swept daily and disinfected weekends to prevent the rats from being infected in accordance with the standard guide for the care and use of laboratory animals.

Study duration: The preliminary studies, animal acclimatization, ingredients procurement/preparation, administration period, processing, microscopy and evaluation of results lasted for a period of six months (from April to October 2016).

Experimental Substance Preparation: A large quantity of MSG (trade name Ajino-moto) was

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procured from the royal market, Ekpoma. A large volume of experimental stock was prepared by dissolving 15.2grams of MSG salt crystals in 380mls of normal saline which was stored in a clean leak proof bottle. The stock was kept in the refrigerator to prolong the life span of the stock and its constituents.

Substance Administration: The administration of MSG was performed orally by using a 2ml syringe to transport the experimental substance through the oral cavity until it gets to the gut. This was done to monitor and control the quantity of MSG given to the rats unlike when mixed with their water. The weights of the rats were taken weekly to monitor the effects of the MSG on the rat's weights and relevant information was also documented.

Group A (control); received a total of4.8mls of normal saline per day (0.8mls/ rat)
Group B (40mg); received a total of 1.2mls of MSG per day (0.2ml/ rat)
Group C (80mg); received a total of 2.4mls of MSG per day (0.4ml/ rat)
Group D (120mg); received a total of 3.6mls of MSG per day (0.6ml/ rat)
Group E (160mg); received a total of 4.8mls of MSG per day (0.8ml/ rat)

Laboratory Analysis: Weight was measured before and after acclimatization, similar weight measurements were done at the end of every week and average weight recorded accordingly. At the end of the administration period, the rats were rendered unconscious by using chloroform gas and the liver of each rat excised through a mid-line abdominal incision passing through the abdominal wall musculature into the peritoneal cavity. The excised liver was described macroscopically, washed in cold saline, weighed and then fixed in 10% formol-saline for histological processing.

Cut Up Procedure: The excised organ was taken to the cutting room for macroscopic examination were relevant information like the color, size (length, breadth and diameter), weight, cut surface was recorded and a laboratory number was generated for the tissue afterwards using the first alphabet of liver (L) and the group from which the liver was coming from. E.g. LA1, LA2, LB1, LC3, LD6, LE6 etc. Afterwards, the whole liver organs of the experimental rats were dissected carefully; a small representative portion was removed and carefully placed in a tissue cassette carrying the new lab number. The cassette was completely immersed in 10% formol-saline and was sent to the laboratory for processing.

Automatic Tissue Processing: The tissues were processed using the automatic tissue processor according to the processing schedule used in the University of Benin Teaching Hospital (UBTH), Benin, Edo state, Nigeria. The plastic cassettes containing the tissue were processed by passing them through different baths in ascending grades of alcohol as follows; 70% alcohol for 2hours, then 80% alcohol, 90% alcohol, 95% alcohol and Absolute alcohol each for 2hours respectively. The tissues were then passed through Xylene, Xylene II, Molten paraffin wax I and Molten paraffin wax II for two hours each respectively.

After the last timing, the tissues were removed from their plastic cassettes and placed at the center of the metallic tissue mould then filled with molten paraffin wax 2-3°C above its melting point and then put on ice to harden for 15 minutes.

The blocks surface was carefully trimmed to expose the tissue and thereafter, serial sections of 3mm thick were cut using a rotary microtome. Tissue ribbons cut off was picked with a clean grease free slide and few drops of 20% alcohol was placed on the cut sections to help flatten and to remove minor folds from the tissue. The sections were floated in water bath at 55°C, picked up by the use of a clean frosted end slide and thereafter, the frosted end of the slide was carefully labeled with a 2B pencil for easy identification. The slide containing the cut sections were placed uppermost on a hot plate for 40minutes for adequate attachment of the sections to the slide and to also remove water from the slide. Sections were stained with haematoxylin and eosin staining technique to demonstrate for general tissue structure as described by Baker, (1962).

RESULTS

From table 1 below, both the control and test groups (B, C, D, and E) presented no observable changes in fur. On the other hand, there were no comparable changes in skin surfaces on the feet, hand, tail, mouth, ears and eyes. Test groups C, D and E presented signs of aggressiveness as part of their behavior and fecal nature (output, texture and quantity) were different in the entire groups as group C, D and E presented pale, gummy and semi-solid stools. Tests groups C, D and E presented different degrees of degenerative changes, but group E tissue sections in particular, presented degenerative changes in the form of interstitial and sinusoidal congestion as well as increased basophilic cell population (see figures 1 -5).

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However, three deaths were recorded in total during the course of this research; two before administration in group B and C and one death in group E during the second week of administration of which the cause of death was unknown and was not related to the dose administered.

Table 1: Notable Physical Observations of Control and Test rats during the Experiment

OBSERVATIONS	CONTROL	GROUP B (40mg)	GROUP C (80mg)	GROUP D(120mg)	GROUP E(160mg)
Fur color	-	-	-	-	-
Behavioral changes (aggressive)	-	-	+	++	+++
Diarrhea	-	-	+	++	+
Death	-	+	+	-	+
Water rejection	-	-	-	-	-
Birth	++	++	+++	++	+
Physical agility	Active	Active	Active	Very active	Very active
Fecal nature (consistency)	Solid	Solid	Semi solid	Semi solid	Semi solid

Key:+ = present in trace amount; ++= present in moderate amount; +++= present in large amount; =negative (absent)

Table 2: Body weight changes of rats fed with MSG at various intervals

Weights (g)	CONTROL (Group A) (n=5)	Group B (n=5)	Group C (n=5)	Group D (n=5)	Group E (n=5)	P-Value
WBA	140.00±22.36	150.00±0.00	150.00±0.00	150.75±0.00	160.00±22.36	0.32
WAA	195.00±27.38	210.00±22.36	225.00±25.00	225.5±27.38	240.00±41.83	0.17
WK 1	270.00±27.38	260.00±13.39	250.00±35.35	240.50±54.77	220.00±27.38	1.74
WK 2	290.00±22.26	255.00±27.38	250.00±35.35	240.50±54.77	220.00±27.38	0.66
WK 3	280.00±27.38	250.00±0.00	255.00±20.91	260.25±37.91	250.00±35.35	0.43
WK 4	330.00±44.72	260.00±54.77	245.00±11.18	280.00±44.72	255.00±44.72	0.03
TOTAL	250.83±70.24	230.83±47.65	225.83±41.77	235.83±45.41	232.50±47.86	

KEY: Significant: $p < 0.05$; Not significant: $p > 0.05$; WBA: Weight before acclimatization; WAA: Weight after; acclimatization; Values are mean ± Standard deviation; n: number of sample

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Table 3: Organ (liver) weight changes of rats fed with MSG at various intervals

Parameters	GROUP A	GROUP B	GROUP C	GROUP D	GROUP E
$\bar{X}$ ± SD	5.98 ± 1.96	8.06 ± 1.65	8.60 ± 1.57	8.86 ± 1.55	9.16 ± 0.80
Number (n)	5	5	5	5	5

KEY: $\bar{X}$ ± SD: Mean and Standard Deviation; n = number of samples; P value <0.05 (Significant)

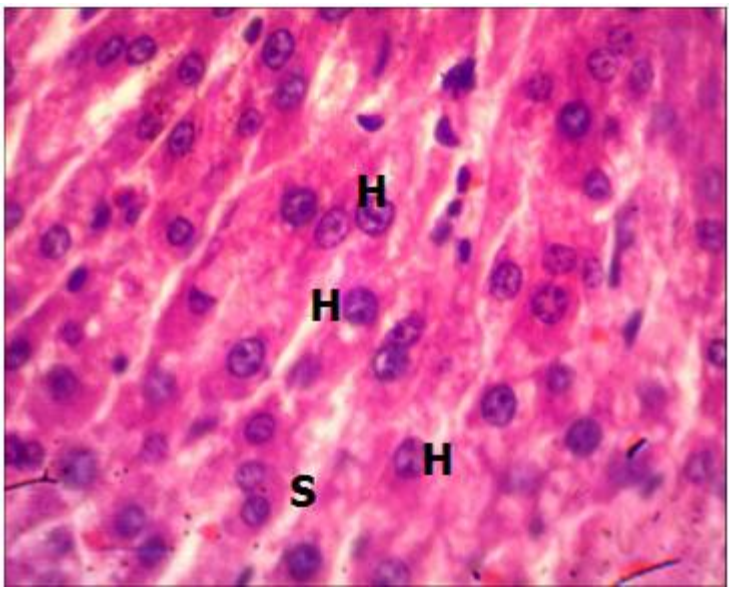

Figure 1: Photomicrograph of group A rats (control) liver section (H & E; x400) showing intact hepatocytes [H] and sinusoids [S].

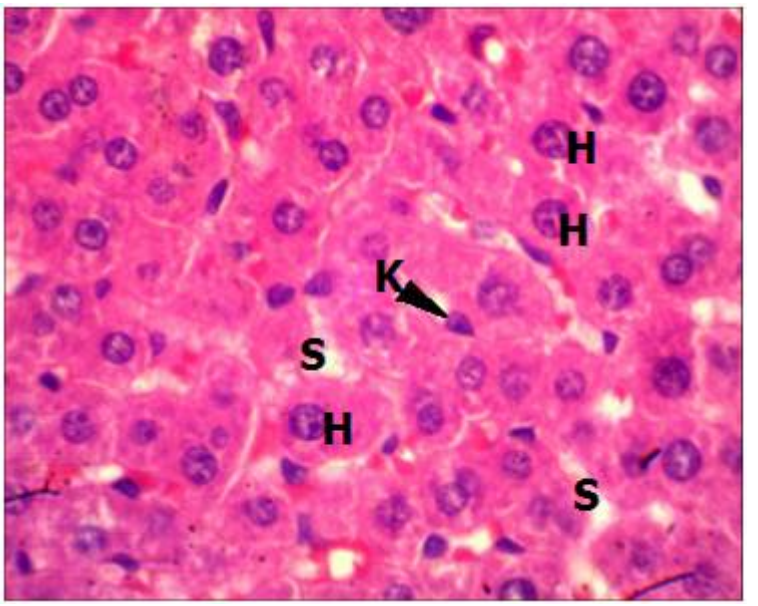

Figure 2: Photomicrograph of test group B rats (40mg MSG) liver section (H & E; x400) showing normal histological features including hepatocytes (H), sinosoids (S) and Kupffer cells (K).

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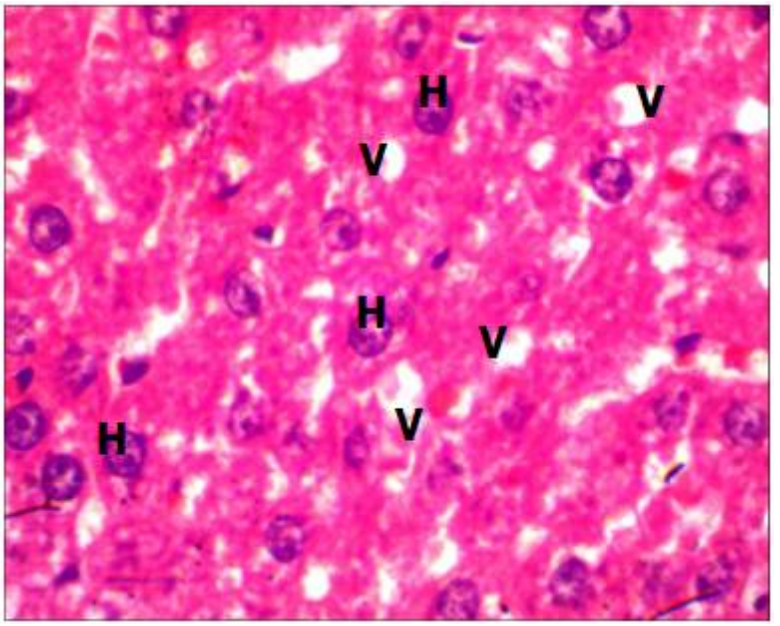

Figure 3: Photomicrograph of test group C (80mg MSG) rat liver section (H & E; x400) showing vacuolations (v) amidst some intact hepatocytes (H).

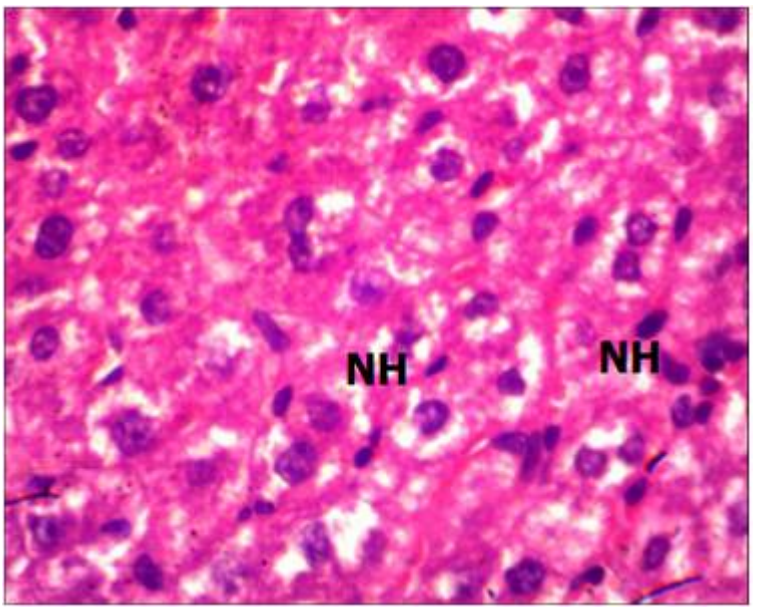

Figure 4: Photomicrograph of test group D (120mg MSG) rat liver section (H & E; x400) showing increased basophilia of necrotic hepatocytes (NH).

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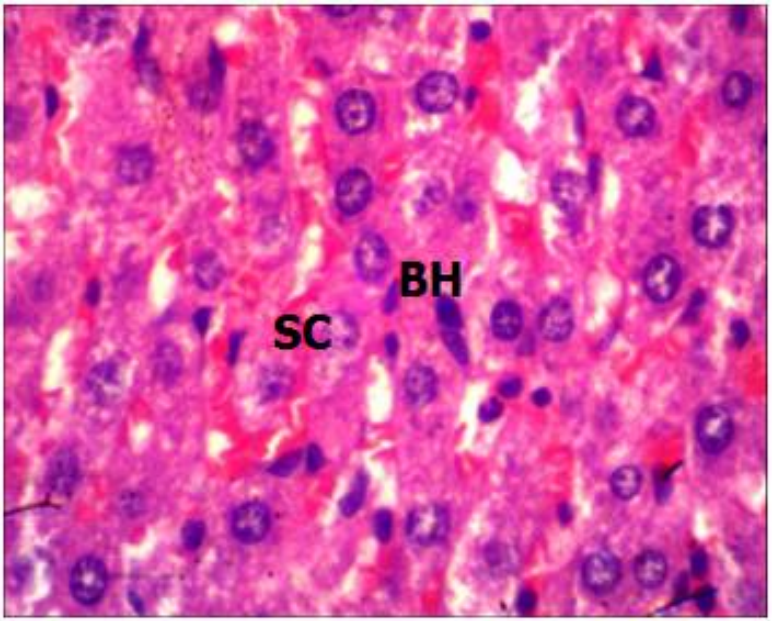

Figure 5: Fig. 4: Photomicrograph of test group E (160mg MSG) rat liver section (H & E; x400) showing degenerative changes with interstitial and sinusoidal congestion [SC] and increased basophilic cell [BH].

Table 2 above, presents the body weight changes in the test and control groups. Although at every stage of the weight determination, the control group (group A) presented weight gain while the test groups (group B, C, D and E) presented a drop in weight. After acclimatization, body weights were found to increase linearly with highest increase observed in group E (240.00±41.83).

After the first week of administration, linear weight gain was observed in group A, B, C and D but a drop in weight was observed in group E (220.00±27.38).

At the second week of administration, weight gain was observed in the control, while the weight across the tests groups remained constant but a small weight loss was observed in group B (255.00±27.38).

At the third week of administration, there was a slight fluctuation in the weights of the animals across the control and test groups.

Finally, at the 4th week of administration, weight gain was observed in the control (group A) and across the test groups; but with a slight reduction observed this time in group C (245.00±11.18).

Comparatively, the weekly body weight variations were found to be significant ($p<0.05$) only at the fourth week of administration.

From table 3 above, the data analysis showed a significant increase in organ weights in the test groups that received 40mg, 80mg, 120mg and 160mg of MSG for a period of 28days (groups B, C, D and E respectively), compared to the control group that received just normal saline. These weight increases were dosage dependent

DISCUSSION

Monosodium glutamate (MSG) is consumed in considerable amounts in almost all forms of food in Nigeria. MSG is one of the most extensively researched food additives in the world and also has a record of being the most controversial food additive in the entire universe (JECFA, 2004 and FASEB, 1995). The findings on body weight, organ (liver) weight and histological changes were in conformity with findings from previous studies.

Findings from this study revealed reductions in weight despite continued increase in food consumption across the test groups. The decrease in

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body weight as noticed in test groups B - E was in line with the reported findings of Shi *et al. (*2010).

However, the findings of this study on weight reduction obviously contradicted the reports from some previous animal studies suggesting a positive link between MSG and obesity; were weight gain was found to be significantly greater in MSG treated animals compared to the control. This could be correlated with increased appetite or even and improvements in the palatability of food via the exertion of a positive influence on the appetite centre (Hermanussen and Tresguerres, 2003; Hermanussen *et al.,* 2006).

A significant increase in the organ (liver) weights of test groups (B, C, D and E) was observed across test groups compared to the control liver. This organ (liver) weight increases corresponds to the progressive increase in the MSG concentration that could be as a result of inflammatory activity with resultant tissue oedema consistent with the results in liver histology that revealed a lot of inflammatory cells (Tawfik *et al.,* 2012).

The cytoarchitectural structure of the liver of group B (40mg) was very similar to that of the control but mild changes in the morphology of test group C (80mg of MSG) was observed. Dilated congested central vein in test group D and E who received 120mg and 160mg, inflammatory basophilic and neutrophilic infiltration in the portal areas of test group D and E, sinusoidal congestion and dilation in test group D and E and degenerative changes were also observed in test group D and E respectively. These findings are in conformity to previous studies by Eweka *et al.,* 2001; Egbuono *et al* 2009; Bhattacharya *et al.,* 2013; Ortiz *et al.,* 2006 and Onoalapo *et al* 2013. However, there was no study to disprove or to trivialize structural changes in the histology of the liver occasioned by MSG.

The myriad effects of MSG as observed in the liver could have occurred because the liver organ is essentially involved in the metabolism of glutamate and is also exposed to many injurious agents and chemical insults. The changes observed in the liver histology may be due to liver exacerbation of trans-fat induced fatty liver disease in mice by a mechanism that includes increased central adiposity and alterations in both hepatic and white adipose tissue gene expression (Collins *et al.,* 2009). Under normal conditions, humans can metabolize relatively large quantities of glutamate, which is naturally produced in the gut in the course of protein hydrolysis. The median lethal dose (LD_{50}) is between 15 and 18g/kg body weight in rats and mice, respectively, five times greater than the LD 50 of salt (3 g/kg in rats), Although some research has shown that the use of MSG as a food additive and the natural level of glutamic acid in foods are not of toxicological concerns in humans (Walker and Lupien, 2000); but close regulation and monitoring of it intake is essential.

CONCLUSION

The findings of this study reaffirm MSG capacity to induce deleterious changes in tissue, while suggesting its capacity to induce alterations in organ and body weights.

RECOMMENDATION

It cannot be denied that monosodium glutamate gives food a unique taste making it sweeter and more palatable. However, we recommend that safer methods of MSG production should be developed, while also recommending moderate MSG consumption.

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