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EVALUATION OF MONO SODIUM GLUTAMATE INDUCED HEPATOTOXICITY IN ADULT WISTAR ALBINO RATS

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ABSTRACT

The main significance of this research is to investigate the effect Mono Sodium Glutamate (MSG) on the liver of Wistar albino rats on a daily intake for a different time interval. Forty Wistar albino rats of body weight 200±30 gm (6-7 month old) were used in the present study. All the animals acclimatized for one week in standard laboratory condition. After acclimatization all the animals were divided into four groups of five male and five females i.e. one control and three treatment groups. Group I served as a control and received normal distilled water while group II, III and IV received MSG at the dose level of 70 mg/100 gm of body weight daily for a period of 30 days, 45 days and 60 days, respectively. At the end of the experimentation, all the animals were sacrificed and the liver was removed, weighed and processed for histopathological examination. The blood sample was also collected from rats on day 31st for group I and II, day 46th for group III and day 61st for group IV from the direct heart puncture of each animal in sterilized EDTA and heparin vial for haematological and biochemical observation.

The Wistar albino rats treated with the MSG showed varying degree of toxicological consequences but these consequences were more severe in that group of animals that received MSG for a long period of time duration.

Decreased in body weight observed in that group of animals who received MSG at the dose level of 70 mg/100 gm of body weight for a period of 60 days. However, decrease in

Haemoglobin, PCV and Neutrophill was also observed in group III and group IV (MSG at the dose level of 70 mg/100 gm of body weight for a period of 45 days and 60 day). The value of RBC was also decreased in the group IV (MSG at the dose level of 70 mg/100 gm of body weight for a period of 60 days). However the value of WBC was significantly increased in the animal of group III and group IV.

In the biochemical parameters, the value of SGPT and SGOT was significantly increased in the group III and group IV (MSG at the dose level of 70 mg/100 gm of body weight for a period of 45 and 60 days). BUN and Creatinine were significantly increased in the group IV animals.

Liver histopathology showed loss of liver architecture, cell death, dilation of central vein, highly dialated sinusoidal space with thickened tunica media and pyknotic cells.

KEYWORDS: Hepatotoxicity, Mono Sodium Glutamate, Wistar Albino Rats.

INTRODUCTION

Monosodium glutamate (MSG) is also known as sodium glutamate. It is the sodium salt of glutamic acid, one of the most abundant naturally occurring non-essential amino acids.[1] It is classified by the U.S. Food and Drug Administration as generally recognized as safe (GRAS) and by the European Union as a food additive. MSG has the HS code 29224229 and the E number E621. Industrial food manufacturers use MSG as a flavor enhancer because it balances, blends and rounds the total perception of other tastes.[2, 3]

The liver plays an important role in the metabolism of glutamate, some glutamate is converted into lactate while the kidney takes part in its elimination although some MSG is metabolized by conversion into alanine in the intestinal mucosa. Some histological changes were noticed in the liver and kidneys of some of the animals randomly selected necessitating a full evaluation of its effect on liver and kidney microanatomy at doses well below those known to be toxic. Nakanishi *et al.*[4] showed that exposure to large doses of monosodium glutamate administered to neonatal rats may result in steatohepatitis and evidence of pre-neoplastic changes in the liver. More recently, chronic exposure to low dose MSG has been shown to result in damage to pancreatic structures including necrotic, degenerative changes to pancreatic exocrine and endocrine cells.

MATERIALS AND METHODS

Collection of Monosodium glutamate

Monosodium glutamate was procured from local supplier in the amount of 500 gm as it is easily available in the local market.

40 Healthy Wistar albino rats were selected for the experimentation. The average weight of each animal is 200 ± 30 gm. All the animals acclimatized for one week in standard laboratory condition.

Study design

Group-I – Included ten rats (five male and five female) that were given a daily oral dose of only distilled water at the dose level of 5 ml/kg body weight for a period of 30 days.

Group-II – Included ten rats (five male and five female) that were given a daily oral dose of MSG at the dose level of 70mg/100 g body weight for a period of 30 days and they were sacrificed.

Group-III – Included ten rats (five male and five female) that were given a daily oral dose of MSG at the dose level of 70mg/100 gm body weight for a period of 45 days.

Group-IV – Included ten rats (five male and five female) that were given a daily oral dose of MSG at the dose level of 70mg/100 gm body weight for a period of 60 days.

Table – 1 Distribution of groups

Groups	Dose (mg/g b.wt.)	Treatment days
Group – 1 control group	Distilled water (5 ml/kg b.wt.)	30 days
Group – II MSG 70 mg/100 gm of body weight	MSG- 70 mg/100 gm of body weight	30 days
Group – III MSG 70 mg/100 gm of body weight	MSG- 70 mg/100 gm of body weight	45 days
Group – IV MSG 70 mg/100 gm of body weight	MSG- 70 mg/100 gm of body weight	60 days

Preparation and administration of test compound

The preparation of test compound Monosodium Glutamate (MSG) was done freshly, few minute prior dosing. The test substance was dissolved in distilled water to obtain final concentration. The animals were dosed by oral gavages at approximately the same time each

day where possible, using a graduated syringe and a stainless steel intubation cannula. The dose volume for each animal was 10 ml/kg body weight (Fig. 1).

OBSERVATIONS

The following parameters were studied.

Mortality

All the animals were observed daily for any mortality up to day 30th for group I and II, day 45th for group III and day 60th for group IV.

Clinical Signs

All the animals were observed at least twice daily to record any symptoms of ill-health or behavior changes. The clinical observations include – changes in skin and fur, in the eyes and mucosa membrane, in the respiratory, circulatory, central nervous and autonomous system and behavior. Clinical signs were graded as follows 0 = No clinical signs, + = mild, ++= moderate, +++= high, ++++= severe.

Body weight

The body weight of each rat was recorded before the start of experiment and after that every week up to the end of the experiment. The mean body weights of different groups and sex were calculated from the individual weights.

HAEMATOBIOCHEMICAL STUDY

Haematological study

The following estimations, with their units of measurement as listed below, were performed using Coulter ACT diff' Haematology Analyzer.

Haemoglobin (Hb) (g/dl), Packed cell volume (PCV) (%), Total red cell count (Total RBC) (x106/cmm), Total white cell count (Total WBC) (x103/cmm), Platelet Count, Total (Platelets) (x103/cmm), Mean corpuscular volume (MCV) (fl), Mean corpuscular hemoglobin (MCH) (pg), Mean corpuscular hemoglobin concentration (MCHC) (g/dl), Clotting time measurement (seconds) was performed manually using standard techniques, Differential WBC counts were determined by microscopy of blood smear, stained with-Wright's stain, counting 100 cells – Neutrophils (N) %, Lymphocytes (L) %, Eosinophils (E) %, Monocytes (M) %.

Biochemical study

Plasma chemistry parameters, with their units of measurement as listed below, were analyzed using the "Erba Smart lab Random Access Batch Analyzer/Erba EC5 Plus Analyzer" (Transasia Bio-Medicals Ltd., India) using standard methodology:

Total Protein (g/dl), Total Cholesterol (Cholesterol) (mg/dl), Albumin (g/dl), Triglycerides (mg/dl), Creatinine (Creatinine) (mg/dl), Alanine aminotransferase (ALT) (IU/L), Urea Nitrogen (UN) (mg/dl), Aspartate aminotransferase (AST) (IU/L), Bilirubin (mg/dl), Glucose (mg/dl).

Terminal Studies

On completion of the study all the animals were sacrificed by CO_2 inhalation. A full necropsy was performed on all animals which included examinations of the external surface of the body all orifices, thoracic and abdominal cavities and their content.

Absolute organ weight

The organ weight of liver of each rat was recorded on different days such as on day 31st for group I and II, on day 46th for group III and on day 61st for group IV. The organs were weighed using a Citizen Electronic Weighing Machine, CY-220-MP-300.

Histopathological examinations

After scarification and dissection, the specimen of livers was removed immediately and fixed in 10% buffer formal saline for 24 hours, then washed and dehydrated in ascending grades of alcohol. After fixation, livers were embedded in paraffin blocks and processed for the preparation of 5 µ thickness sections with the help of YSI-115 Precision Rotary Microtome. These sections were subjected for following stain; Hematoxylin and Eosin (H & E).

STATISTICAL ANALYSIS

All the data were analyzed using the one way analysis of variance (ANOVA) followed by Tukey HSD test carried out to determine the source of a significant effect. Results were expressed as Mean ± S.E.M., $p<0.5$ is taken as accepted level of significant difference from control.

RESULTS

Haematological parameters

The haemoglobin concentration was statistically significant decrease ($p<0.05$) in both the group III and group IV in comparison to control whereas the concentration of RBC was

significantly decrease ($p<0.05$) in group IV. WBC was significantly increase ($p<0.05$) in group III and IV.

The value of mean corpuscular volume (MCV) and Packed cell volume (PCV) was observed high in the group IV (MSG at the dose level of 70mg/100 gm of body weight for a period of 60 days). However the value of Mean corpuscular haemoglobin concentration (MCHC) was decreased in the group IV when compared to control group. The value of Neutrophils was decrease significantly ($p<0.05$) in groups III and IV. Furthermore, the value of lymphocytes was significantly increase ($p<0.05$) in groups III and IV.

Table for haematological parameters is listed below:

TABLE – 2

SUMMARY OF HAEMATOLOGY

Parameters	**GROUPS**			
	Group-I Distilled water (5ml/kg body weight)	**Group-II MSG 70 mg/kg body weight for 30 days**	**Group-III MSG 70 mg/kg body weight for 45 days**	**Group-IV MSG 70 mg/kg body weight for 60 days**
Haemoglobin (Hb) (g/dl)	13.74±0.77	13.83±0.53	12.2±0.71*	10.24±0.31*
Total red cell count ($x10^6$/µl)	7.43±0.50	7.52±0.55	7.74±0.61	5.78±0.93*
Total white cell count (Total WBC)($x10^3$/µl)	11.8±0.55	11.77±0.47	14.45±0.78*	15.01±0.97*
Packed cell volume (PCV) (%)	44.12±0.50	44.04±0.73	43.11±1.01	38.78±1.04*
Mean corpuscular volume (MCV) (fl)	59.57±3.88	58.56±4.18	55.69±3.77	67.33±2.05*
Mean corpuscular haemoglobin (MCH) (pg)	18.56±1.66	18.46±1.74	15.76±1.62*	17.71±1.46
Mean corpuscular haemoglobin concentration (MCHC) (g/dl)	31.15±1.88	31.38±1.59	28.29±2.12*	26.30±1.32*
DIFFERENTIAL LEUCOCYTE COUNT (%)				
Lymphocyte	76±1.03	75±1.41	85±1.03*	87±7.68
Neutrophils	21±0.94	22±1.31	13±3.06*	12±2.14*
Monocytes	1±0.73	1.0±0.73	1±0.63	1.0±0.48
Eosinophils	2±0.66	2.0±0.69	1.0±0.78	1.0±0.94

Data are expressed as Mean ± S.D. (n=10)

Values are statistically non significant from control (P> 0.05)

BIOCHEMICAL STUDY

At the end of the experiment all the animals were sacrificed and blood samples were withdrawn from direct cardiac puncture in glass tubes. Serum was separated by centrifugation for 10 min at 4000 rpm and stored at -40 ^{o}C until biochemical analysis. The following parameters were done from the serum sample.

The biochemical parameters Total and Direct Bilirubin, Total Protein and Glucose did not show any significant ($p>0.05$) change in their value when compared to the value of control group. However the values of Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Aspartate aminotransferases and Blood urea nitrogen (BUN) were found high in both the group III and IV. Albumin and Creatinine level was also high in the group IV animals.

TABLE – 3

SUMMARY OF BIOCHEMICAL CHANGES (Mean±SE)

Parameters	GROUPS			
	Group-I Distilled water (5ml/kg body weight)	**Group-II MSG 70 mg/kg body weight for 30 days**	**Group-III MSG 70 mg/kg body weight for 45 days**	**Group-IV MSG 70 mg/kg body weight for 60 days**
Albumin (g/dl)	3.66±0.030	3.57±0.52	3.70±0.05	5.53±0.06*
Total Protein (g/dl)	7.07±0.07	6.82±0.26	6.54±0.13	6.60±0.09
Bilirubin total (mg/dl)	0.44±0.02	0.45±0.021	0.48±0.025	0.47±0.01
Bilirubin Direct (mg/dl)	0.14±0.013	0.13±0.013	0.16±0.010	0.16±0.09
Alanine Aminotransferase (ALT) (IU/L)	21.57±0.09	23.19±0.095	27.48±0.12*	29.49±0.27*
Alkaline phosphatase (ALP) (IU/L)	80.35±0.57	85.72±0.08	65.30±0.09*	60.06±0.10*
Aspartate aminotransferase (AST) (IU/L)	83.02±0.02	89.71±0.10	96.82±0.08*	101.21±0.10*
Blood Urea Nitrogen (BUN) (mg/dl)	22.86±0.088	25.17±0.31	30.65±0.092*	32.14±0.067*
Creatinine (mg/dl)	0.21±0.017	0.21±0.016	0.23±0.013	0.27±0.012*
Glucose (mg/dl)	114.9±0.14	110.85±1.93	109.95±0.32	109.97±0.17

Data are expressed as Mean ± S.D. (n=10)

Values are statistically not significant from control (P> 0.05)

Absolute organ weight

At the next day of end of the dose administration the specimens of liver from the all dose groups were removed, washed in ice-cold 1.15% KCI solution to remove blood and other extraneous substances, dried in a filter paper and weighed. There was no change recorded in

the weight of liver of group II and group III as compared to group I (control group). Whereas, the weight of liver was increased in the group IV as compared to control group.

Table 4: Organ Weight

Groups	liver
Group-I **Distilled water control**	5.23±0.14
Group-II **MSG 70 mg/kg body weight for 30 days**	6.21±0.24
Group-III **MSG 70 mg/kg body weight for 45 days**	5.31±0.17
Group-IV **MSG 70 mg/kg body weight for 60 days**	9.13±0.21*

*p<0.05 as compared to control

Necropsy finding

On completion of the study (day 31st for group I and II and day 46th and 61st for group III and IV) all the animals were sacrificed by CO_2 inhalation. A full necropsy was performed on all animals which included examinations of the external surface of the body all orifices, thoracic and abdominal cavities and their content.

No gross pathological changes were observed in the liver of MSG treated group II and III. However, mild congestion and increase in weight was observed in the group IV (MSG at the dose level of 70mg/100 gm body weight for 60 days).

Histopathological findings

The rats were sacrificed at the end of the dose administration (such as day 31st for group I and II, day 46th for group III and day 61st for group IV). The tissues of livers were quickly dissected and fixed in 10% formal saline for routine histopathological technique.

The tissues were dehydrated in an ascending grade of alcohol (ethanol), cleared in xylene and embedded in paraffin wax. Serial sections of 5 microns thick were obtained using a rotator microtome. The deparafinised sections were stained routinely with haematoxyline and eosin. Photomicrographs of the desired results were obtained using digital research photographic microscope.

The individual histopathological findings of all groups were as follows:

Group I – This group includes ten Wistar albino rats (5 male and 5 female) and only distilled water given to this group for a period of 30 days. Necropsy of this group was conducted on

day 31st and the **tissues** of livers were dissected from the animals. As this group served as a control group, no microscopic changes were recorded in liver (Fig. 1).

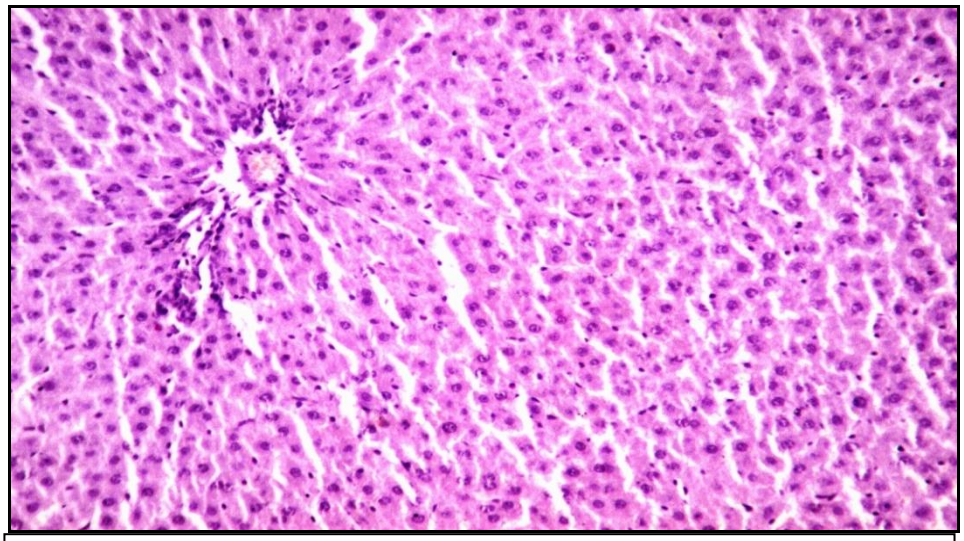

Fig-1 T.S. of liver showing normal structure in vehicle control group of wistar albino rats. H&E 10×10X

Group II – This group includes ten Wistar albino rats (5 male and 5 female) and this group of animals were treated with the Monosodium glutamate (MSG) at the dose level of 70mg/100 g body weight for a period of 30 days through oral administration and they were sacrificed on day 31st.

Examination of liver sections of this group of animals showed mild disturbance of liver architecture, small necrotic areas with mold vacuolation, enlarged and congested central vein (Fig – 2).

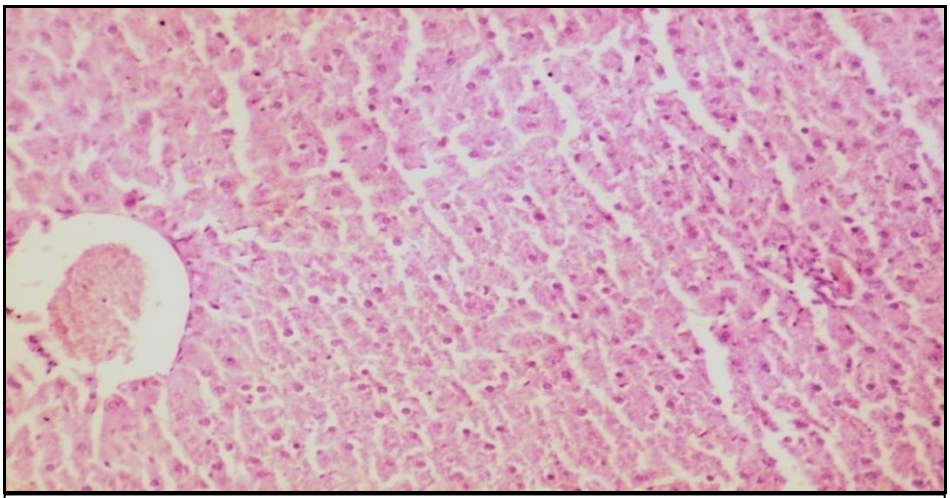

Fig – 2 T.S. of liver showing change in cellular architecture, small necrotic areas and congested central vein in wistar albino rats treated with Monosodium glutamate (MSG) at the dose level of 70mg/100 g body weight for a period of 30 days. H&E 10×10X

Group III – This group contains ten Wistar albino rats (5 male and 5 female) and they were given a orally administration of MSG at the dose level of 70 mg/100 gm body weight for a period of 45 days and they were sacrificed and the tissues of livers were dissected and subjected to microscopical changes.

Microscopic examination of liver tissue showed loss of liver architecture with varying degree of liver parenchymal disorganization, cell death, dilation of the central vein and presence of inflammatory cells within and around the central vein. There were also variations in the sizes and shaping of the nuclei, vacuolation, pyknosis and most nuclei are atrophied (Fig – 3).

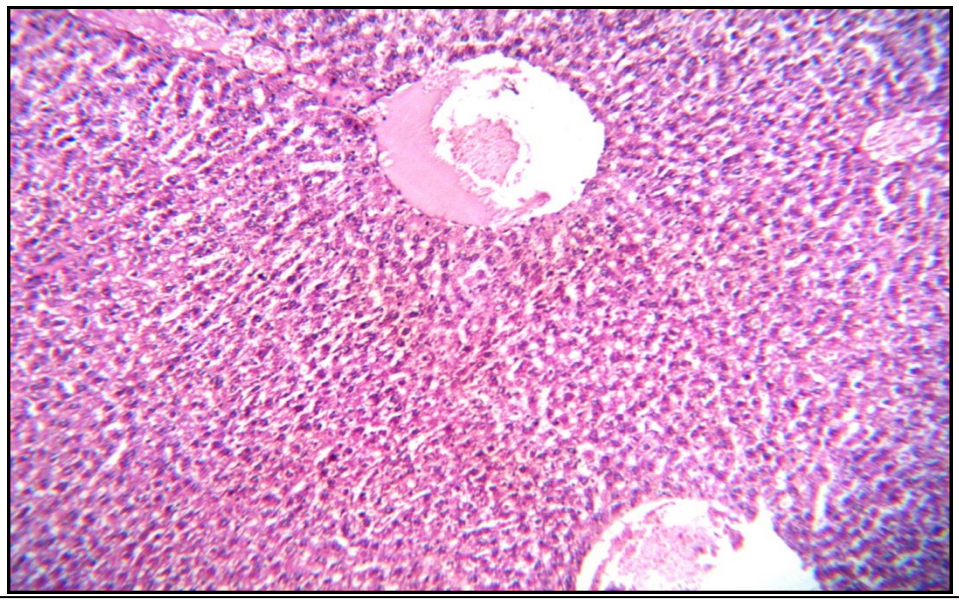

Fig – 3 T.S. of liver showing change in cellular architecture, dilation of central vein, vacuolation, pyknosis and atrophied nucleus in wistar albino rats treated with Monosodium glutamate (MSG) at the dose level of 70mg/100 g body weight for a period of 45 days. H&E 10×10X

Group IV – This group also contains 10 Wistar albino rats (5 male and 5 female). This group of animals received MSG through oral administration for a period of 60 days at the dose level of 70 mg/100 gm of body weight. The animals of this group were sacrificed on day 61st.

The microscopic examinations of liver revealed that disturbed liver architecture hemorrhage, areas of necrosis, and increased vacuolation most nuclei are atrophied. In addition to these changes congested central vein with highly affected endothelial lining which contained hypertrophied nuclei, highly dilated sinusoidal spaces with thickened tunica media and pyknotic cells. (Fig – 4).

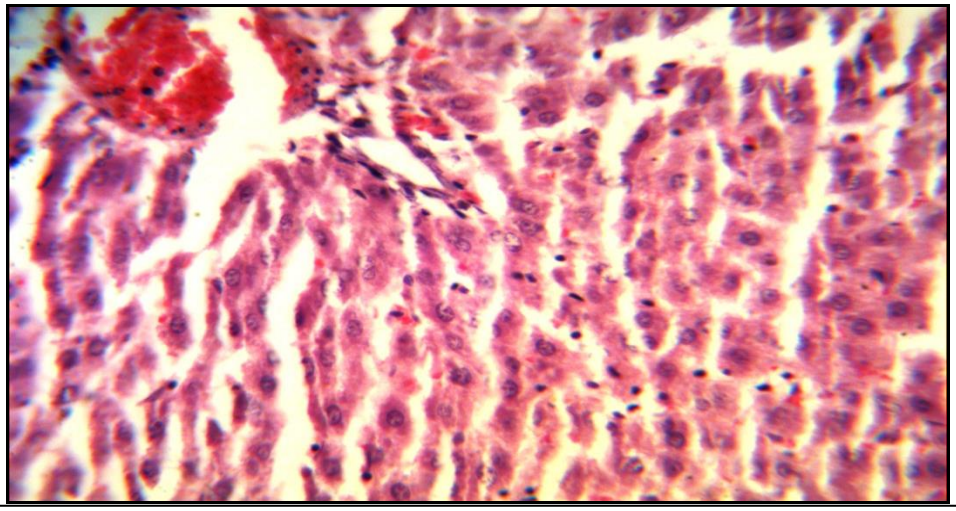

Fig – 4 T.S. of liver showing change in cellular architecture, congestion of central vein, vacuolation, pyknosis and atrophied nucleus in wistar albino rats treated with Monosodium glutamate (MSG) at the dose level of 70mg/100 g body weight for a period of 60 days. H&E 10×10X

DISCUSSION

Monosodium glutamate (MSG) is one of the most frequently applied additives in the developed world.[5] Modern nutrition enables a continuous intake of the flavor enhancer with resulting ruse and accumulations of GA (glutamic acid) in blood.[6] Several studies showed toxic effects of MSG in various region of the CNS.[7] Liver and kidney mainly by generation of the reactive oxygen species (ROS) and resulting oxidative stress. In MSG sensitive individuals, the adverse effects are observed even at doses recommended in food.[8] Furthermore, disruption in the levels of biochemical parameters such as ALT, AST, Albumin, Creatinine, ALP etc. in MSG treated rats has also been well documented.[9] Chronic administration of MSG (4 mg/g body weight and above) was found to induce oxidative stress in experimental animals.[10, 11]

The present study revealed that the ingestion of MSG was deleterious causing degeneration, vacuolation, cellular infiltration and fibrosis in the liver. These results were in accordance with that report who stated that the histopathological changes on rat liver and kidney fed with monosodium contaminated food. They found that there were foci of necrosis, fatty degeneration and micro vascular changes in the liver. In the kidney, patchy tubular necrosis and interstitial infiltration were present.[12]

The most marked signs of liver tissue impairment and vacuolation in the present study were observed in centrolobular hepatocytes zones than portal zones hepatocytes in all treated

groups. These results agree with the work where it was noted that the vacuolation of hepatocytes were more pronounced around the central vein in the mice injected by MSG for 75 days.[13]

The centrolobular hepatocytes are typically the primary site of toxins, they have more surface receptors for toxins and less oxygen.[14] The vacuolation of hepatocytes as ballooning degeneration and interpreted it as a kind of cellular defensive mechanism against injurious substances.[15] These vacuoles are responsible for collecting the injurious elements and preventing them from interfering with the biological activities of these cells.

Current work revealed pyknosis and karyolysis of cell nuclei may indicate the loss of functional efficiency of the cells. Similar results have been demonstrated on male rats obtained 4mg/kg of MSG.[16] Also, this result is consistent with the findings that indicating hypertrophy of nuclei and pyknotic nuclei in MSG treated chick.[17] In agreement with these results it has been stated that the cells lining the bile ducts are stem cells that activated and prolifered with necrosis or lysis of liver cells.[18]

Monosodium glutamate (MSG) increases the glycogen content of the liver cells because its administration was associated with hyperglycemia and hyperinsulinema. Monosodium glutamate induced alteration in metabolic rate or glucose utilization and decreased antioxidant defenses. The oxidative stress induced by MSG intake caused remarkable formation of collagen fibres in the liver cells.

In the biochemistry of liver, significant increase in the alanine amino transferase **(**Group – 1 21.64±3.16, Group – II 23.19±3.34, Group – III 27.49±2.42, Group – IV 29.52±2.33) and aspartate aminotransferase (Group – 1 83±9.65, Group – II 89.79±6.92, Group – III 96.81±4.75, Group – IV 101.18±3.71) and alkaline phosphatase (Group – 1 80.35±15.34, Group – II 85.85±6.92, Group – III 103.26±3.19, Group – IV 107±10.97) was observed in the MSG treated rats as compared to control group. The ALT enzyme is the sensitive marker of liver damage. Therefore, the increase in the serum ALT activity observed in the rats of Group – II and Group – III perhaps be an indication of liver damage. MSG could dissociate easily to release free glutamate. The deamination of GLU produces ammonium ion that could be toxic unless detoxified in the liver via the reactions of the urea cycle. Thus the possible ammonium ion overload that may occur as a result of an increased level of glutamate following MSG

intake could damage the liver, consequently releasing the AT enzyme that may lead to its observed elevation.

The result seemingly agrees with the reports in which the activity of serum AT increased in male rats that were fed MSG probably due to MSG induced oxidative stress in the liver.[19] Thus it could be concluded that MSG may be hepatotoxic at a low dose, hence should be avoided during the treatment of liver disorders. Furthermore, since ALT was a strong positive indicator insulin resistance, diabetes mellitus and obesity,[20] which are risk factors for coronary heart disease.[21, 22] The use of MSG at a low dose should not be encouraged because of the possible untoward health implications.

An increase in the serum AST activity was observed in rats that were given MSG orally, probably predicting damage to the liver and other organs with high metabolic activity (including the brain, heart and lungs) as previously reported.[23] In addition, the observed increase in the serum AST activity may be indicative of myocardial infarction.[24] The observation agrees with the previous reports that the activity of serum AST increased in male rats that were fed MSG due to MSG induced oxidative stress.

MSG treated rats increased the serum AST-ALT indicating possible cirrhosis (hardening) of the major organs.[25] This appears to suggest the inherent risk in the use of MSG even at a low dose in rats. Therefore, caution should be exercised in the use of MSG over time till further studies are carried but to elucidate the effect in humans.

The decreased in the serum ALP activity observed in the rats that were dosed with MSG at the tested dose level (70 mg/100 gm of body weight for 45 days and 60 days), may indicate possible absence of adverse effects of MSG intake on the pathologies of the bone since increased serum ALP activity has been associated with bone deceases.[26] The significant reduction in the ALP activity by MSG may perhaps indicate the absence of cholestasis (lack of bile flow). Cholestasis may result from the blockage of the bile duct or from a disease that impairs bile formation in the liver itself. Thus the possible absence of cholestasis with MSG intake could not be explained by the observation in the present study of possible liver damage in rats that were given MSG as indicated by increased serum SLT and AST activities.

However, increase in the markers of liver damage without an increase in the marker of cholestasis have been reported in rats and interpreted as evidence of ongoing hepatocellular toxicity of the absence of significant cholestasis.[27]

Therefore, that the consumption of MSG even at a low concentration may promote the induction of oxidative stress in the liver which may, as a consequence, lead to liver damage. This may further suggest that MSG could be an oxidant or may not be effective in scavenging the reactive oxygen species, hence should be avoided in the prevention and management of oxidative stress. These reported adverse effects of MSG suggest that the use of this substance as a flavor enhancer over time may be hepatotoxic. Therefore, the present study was aimed at determining whether MSG intake at a low dose could be toxic on selected hepatocellular functions of male albino rats.

CONCLUSION

From the present study, it can be concluded that the deleterious effects of Monosodium Glutamate (MSG) on liver were duration and concentration related. There was a highly significant changes observed in that group of animals which received Monosodium glutamate for a longer time (group III and group IV). Also there was a marked increase in the weight of liver of group IV animals.

Various Histopathological and biochemical changes were also recorded in the animals that received Monosodium glutamate for a longer time. Hence, based on the results, it can be concluded that the deleterious effects of Monsodium glutamate were concentration and duration related.

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