Original article

The Toxic Effect of Monosodium Glutamate on Liver and Kidney Functions in Wister rats

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Abstract

Monosodium Glutamate (MSG), locally known as "Maggi" is one of the worlds' most widely used food additives. It is used in modern nutrition worldwide as a flavor enhancer. MSG is widely used by Sudanese families and recently it becomes very popular in rural areas due to its availability and low price especially under the harsh economic situation of the country. Fifteen, 3-month old, both sexes Wister rats were randomly assigned into three groups. Control, low dose (5mg/kg/day) and high dose (15mg/kg/day) of monosodium glutamate, were administered orally to Wister rats weighing between (85-100 g) for 4 weeks. Liver and Kidney function tests were carried out on the blood serum. Hematological parameters where also tested and Necropsy was conducted to identify gross lesions in liver, kidney and intestine. The results show that monosodium glutamate induced an increase in body weight and significant change in the activity of liver enzymes (ALT, AST and ALP). Also, there was a significant increase in WBCs, the level of total protein and globulin, as well as increase in creatinine and Urea. Histopathological examination showed clear changes in liver, kidney and intestine tissues. These findings revealed that Monosodium glutamate consumption may have toxic effects in liver and kidney tissues especially when consumed at higher concentrations and continuous consumption may affect the function of liver and kidney.

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Introduction

Food additives are substances that become part of a food product either directly or indirectly during some phase of processing, storage or packaging. Most of the foods on our shelves contain some chemicals and additives that are known to harm either the human body or laboratory animals. Monosodium glutamate (MSG), locally known as "maggi" in Sudan, is one of the world's most extensively used food additives which are ingested as part of

commercially processed foods. It have been used as a flavor enhancer and used as food additive (Afaf *et al.,* 2015).

MSG is the sodium salt of glutamic acid, one of the most abundant naturally occurring non-essential amino acids (Zehra *et al.,* 2017).

. It is the main component of many proteins and peptides, and is present in most tissues. Monosodium glutamate is present in heterogeneous group of foods as a flavor enhancer and used either as food additive in the form of hydrolyzed protein or as purified monosodium salt. For the first time (1908), MSG was discovered in Japan from seaweed as a flavor enhancer (Zehra *et al.,* 2017).

Through its stimulation of the sensory receptors and improving the palatability of the meals, monosodium glutamate influences the appetite positively and induces weight gain (Inuwa *et al.,* 2011). When MSG is added to food, it provides a flavoring function similar to the naturally occurring free glutamate which differ from the four classic tastes of sweet, sour, salty and bitter (Tawfik and Badr, 2012 and Schiffman, 2000).

MSG has been proved to be toxic and associated with adverse side-effects reported by various studies particularly in animals (Oladipo *et al.,* 2015). Evidences suggested that MSG can induce obesity and the potential link between MSG and obesity includes the MSG effect on energy balance by increasing palatability of food and by disrupting the hypothalamic signaling cascade of leptin action (Iwase *et al.,* 2000 and Pinterova *et al.,* 2001).

In a recent study conducted by Nagata *et al.,* The MSG-treated mice showed increased blood glucose, insulin, triglycerides, and cholesterol levels as compared with control animals and MSG-induced diabetic condition in mice was strikingly similar to human type 2 diabetes mellitus (Nagata *et al.,* 2006).

MSG also has proven hepatotoxic and genotoxic effects, consumption of high doses of MSG can develop symptoms of liver damage and genotoxic effects (Nakanishi *et al.,* 2008). Since glutamate was known as an important excitatory neurotransmitter in the central nervous system, its excess leads to excitotoxicity which may cause severe neuronal damage and other complications. High doses of MSG cause neuronal necrosis in hypothalamic arcuate nuclei in neonatal rats (Veronika and Daniela, 2013).

A condition referred to as "Chinese restaurant syndrome" characterized by sweating, nausea, headache, chest tightness, and/or a burning sensation in the back of the neck (Andrew *et al.,* 2010). Furthermore, long- term intake of MSG was shown to induce, asthma, hyperphagia, immune system impairment, memory problems, and damage to hypothalamic neurons (Hassan *et al.,* 2014). Thus, the addition of MSG to foods and the continuous consumption can have serious effects on health.

In Sudan people use MSG as a food additive and sometimes as a bleaching agent. MSG is popular because it is cheap price and widely available in the local markets throughout the country in a form of concentrated salt. There is a growing concern about the safety of MSG, because this food additive could be slowly and silently doing major damage to health. As the dose of MSG increases, every single human will react to MSG at some point and at certain doses it becomes toxic enough to cause illness. Since controversy obviously exists about Monosodium glutamate, and since this material goes on being largely used, the present study was undertaken to further investigate the possible effect of various levels of MSG on liver and kidney functions.

Material and methods

Monosodium Glutamate

Monosodium glutamate in a white granular crystalline form was purchased from a local market in Omdurman and used in the present study (Fig. 1a, b). For the dose preparation, (5 and 15 mg/kg daily) MSG was weighted accurately and then dissolved in distilled water.

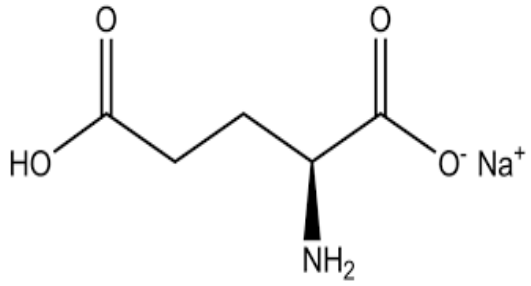

Fig.1a.Structure of Monosodium Glutamate

Fig. 1b. Monosodium Glutamate (Chinese salt)

Experimental Animals

Fifteen, 3-month old, both sexes Wister rats, with average body weight 85-100g were used in this study. The rats were apparently clinically healthy and housed within the premises of Al Neelain University Animal House under standard husbandry conditions of temperature and light (30˚C ± 5, and 12h light-dark cycle) and fed with the rat diet and water provided *ad. Libitum*. Animals were acclimatized to the experimental conditions for a period of one week prior to the commencement of the experiment.

Experimental Design

After one week of acclimation, the rats were divided randomly to three groups, each of 5 rats as follows: Group 1 received distilled water and continued to be fed the normal diet and served as control. Groups 2 and 3 were given 5mg/kg/day and 15mg/kg/day Monosodium glutamate via the oral route, respectively. All rats were given their designated experimental oral doses for 4 weeks.

Body weights of rats were measured weekly for each group. Clinical signs, average body weight and body weight gain were recorded. Blood samples for hematological and serobiochemical analysis and specimens for histopathological examination were immediately collected after scarifying all animals from each group under mild chloroform anesthesia.

Hematological and serobiochemical analysis

Blood samples for measurements of complete blood count (CBC) were collected in EDTA containers and analyzed immediately using Automated HaematologyAnalyser (Sysmex KX-21, Japan, 1999). Blood samples for serum chemistry analysis were collected in plain containers, centrifuged at 350 rpm for 5 min then the serum were separated, properly labeled and stored at -20˚C until used.

Hemoglobin concentration(HB), Red blood cell (RBC), white blood cell (WBC), mean corpuscular Volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin Concentration (MCHC) were estimated.

Serum was analyzed for the activities of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) and for concentration of total protein, albumin, globulin, Urea and creatinine by using commercial kits (Linear Chemicals, Barcelona, Spain).

Histological examination

For histological analysis, Necropsy was conducted and all rats were examined to identify gross lesion. Specimens of the liver, Kidney, and small intestines were collected, immediately fixed in 10% formalin, embedded in paraffin wax. Subsequently, sectioned at 5µm thick with microtome and stained with haematoxylin and eosin (H&E) using Harris's hemalum. Staining was performed at room

temperature and tissues were observed under a light microscope (Andrew *et al.*, 2008).

Statistical analysis

For the analysis of the data, Statistical Package for Social Science (SPSS) was used. The significance of difference between means was compared at each point using Duncan s multiple range tests after ANOVA for one–way classified data. Results are presented as the mean ± standard error. *P*<0.05 was considered to indicate a statistically significant difference (Snedecor and Cochran, 1989).

Results

Growth changes

The effect on body weight of rats given daily oral doses of monosodium glutamate at 5mg/kg/day (Group 2) and 15 mg/kg/day (Group 3) for 4weeks was shown in Table 1 and Figure 2. There were significant changes in the body weight gainsin test rats given daily oral doses of MSG compared to the control group (Group1). All groups show significant increase in week 2. No death among the rats occurred.

Table.1. Body weight and Body weight gain in rats orally given monosodium glutamate for 4 weeks.

Treatment groups	Body weight gain (g)		
	Day 0	2 weeks	4 weeks
1.Control (normal diet)	85.33±0.67	10.0±4.7	20.67±1.2
2. (5mg/kg/day)	90.00±2.00	19.33±2.7*	12.67±7.6*
3.(15mg/kg/day)	91.33±0.67	30±9.8*	0.66±10.7*

Values are expressed as means ± SE; * Significant= (*P*<0.05).

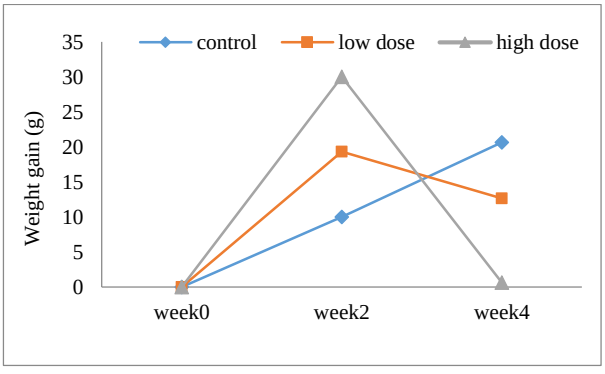

Fig. 2. Body weight gain (g) for rats orally given Monosodium Glutamate different doses compared with control for 4 weeks.

Hematological changes

Hematological changes for rats given daily oral doses of monosodium glutamate at 5mg/kg/day (Group 2) and 15 mg/kg/day (Group 3) for 4weeks are presented in Table 2. The values of Hb, RBCs, WBCs and Neutrophil were increased significantly in all do treated groups with (*P*-value <0.05) compared to the control untreated group. Also, there was significant decrease in mean concentration of Lymphocytes in all MSG treated group when compared with untreated group with (*P*-value <0.05), while other hematological parameters showed no significant change.

Table.2. Hematological changes in rats given MSG orally for 4 weeks.

Parameters	1. Control (normal diet)	2. MSG (5mg\kg/day)	3. MSG (15mg\kg/day)
Hb (g/dl)	9.6±2.22	12.0 ±0.4*	13.7 ±0.4*
RBC (x10^{6}mm^3)	5.4 ± 1.28	6.7 ±0.22*	7.6 ±0.10*
MCV (m^3)	54.6 ±0.78	53.2 ±0.87 ^{NS}	55.7 ±2.51 ^{NS}
MCH (pg)	17.9 ±0.35	17.77±0.03 ^{NS}	17.87±0.80 ^{NS}
MCHC (g/L)	32.80±0.84	33.47±0.58 ^{NS}	32.13±0.09 ^{NS}
WBC (X10^{6}mm^3)	11.2±4.30	17.2±1.90*	13.9±1.58*
Lymphocytes (%)	60.53±2.60	48.67±5.03*	57.30±3.5*
Neutrophils (%)	39.47±1.80	51.33±6.5*	42.7±0.84*

Values are expressed as means ± SE; NS = not significant; *Significant= (*P*<0.05).

Serobiochemical changes

Serobiochemical changes for rats given daily oral doses of monosodium glutamate at 5 mg /kg (groups 2) and 15 mg/kg (groups 3) for 4 weeks are summarized in Table 3 and Figure 3. After 4 weeks of treatment results showed significant increase in the activity of ALP and concentrations of total protein and globulin in all treated groups, while ALT showed significant increase only in group 2 (5mg/kg). AST and albumin showed no significant change when compared with control (group 1). Creatinine and urea concentrations in groups 2 and 3, were significantly increased 30 days after treatment. Four weeks after treatment the concentration of creatinine was higher in group 2 and lower in group 3 than control (group 1). The concentration of urea was higher (*P*<0.05) in all groups compare to control.

Table.3. Changes in serum constituents of rats given MSG orally for 4 weeks.

Parameters	1.control (normal diet)	2. MSG (5mg\ kg)	3.MSG (15mg\kg)
ALP (IU)	10.1±4.1	39.1±14.51*	42.3±15.02*
ALT (IU)	26.6±10.6	36.0±19.53*	9.2±3.23*
AST(IU)	48.8±18.0	33.8±1.47*	36.6±12.58*
Total protein (g/dl)	4.3±0.47	6.84±0.33*	7.48±0.50*
Albumin(g/dl)	2.15±0.22	2.33±0.53^{NS}	2.23±0.51^{NS}
Globulin(g/dl)	2.19±0.55	4.51±0.73*	5.25±0.73*
Urea (mg/dl)	72.99±2.62	91.44±0.44*	77.96±1.49 ^{NS}
Creatinine(mg/dl)	1.3±0.40	2.1±0.17^{NS}	1.2±0.37^{NS}

Values are expressed as means ± SE; NS = not significant;* Significant= (P<0.05)

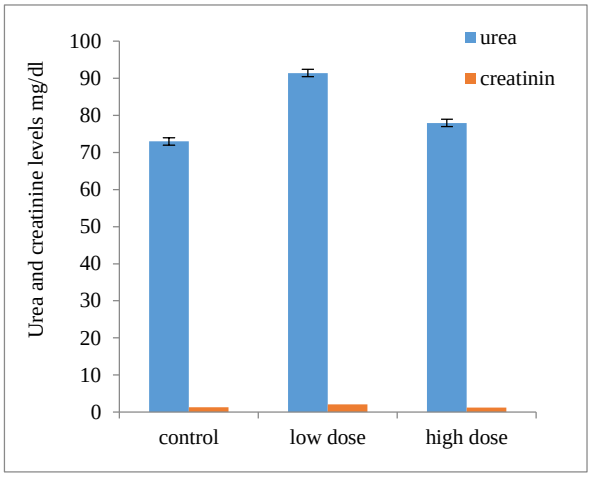

Fig. 3. Effects of various oral doses of MSG on activities of kidney functions. It shows the relationship between the creatinine and urea expressed as mean ± SE.

Pathological changes

After four weeks of treatment with daily oral doses of Monosodium glutamate at 5 mg/kg/day (group 2) and 15 mg/kg/day (group 3) for four weeks showed consistent lesions that included Cytoplasmic fatty vacuolation of centrilobular hepatocytes and isolated cell necrosis in liver (Figure 4). Dilatation of renal tubules in kidney and lesions that included epithelial cell degeneration or necrosis of the renal convoluted tubules of the glomeruli were also detected (Figure 5). Infiltration of lymphocytes in the intestinal lamina proprian were also observed (Figure 6). These changes were less marked in group 2 and no significant lesions were observed in the control rats (group1).

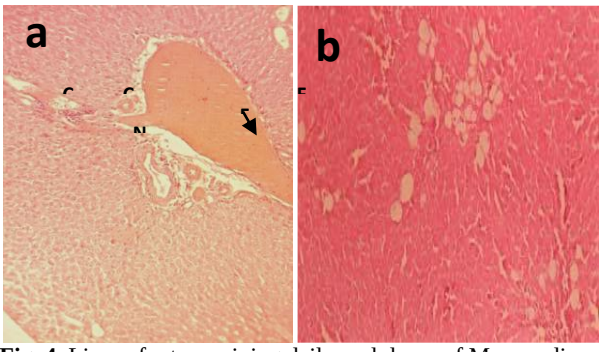

Fig. 4. Liver of rats receiving daily oral doses of Monosodium glutamate 15 mg/kg for 4 weeks showing **(a)** cytoplasmic fatty vaculation and necrosis of the centrilobular hepatocytes, **(b)** fatty vaculation of the interlobular hepatocytes. H & E (X200). CV = central vein, FV = fatty vaculation, N= necrosis, C= congestion

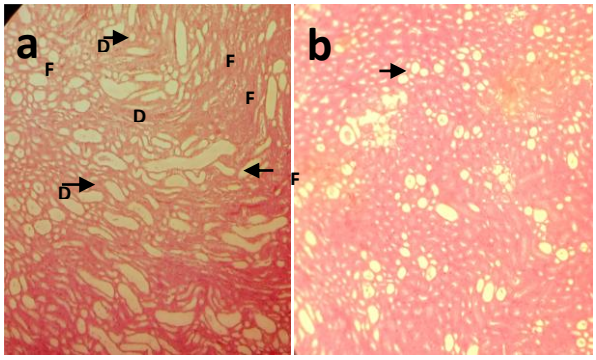

Fig. 5. Kidney of rats receiving daily oral doses of Monosodium glutamate 15 mg/kg for 4 weeks showing (a)dilatation and necrosis, (b) fatty change of renal tubules. H & E (X100). D = dilatation, FC = fatty changes, N= necrosis (black arrow)

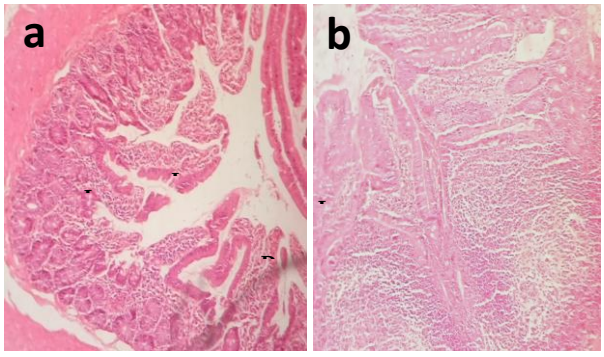

Fig. 6. Intestine of a rats received oral doses of Monosodium glutamate at 15 mg/kg/day for four weeks showing Catarrhal enteritis, lymphocytic infiltration in intestinal lamina Propria and desquamation of the intestinal epithelium .(a) H&E X100,

(b) H&E X200. LI = lymphocytic infiltration, D = desquamation,,LP= lamina Propria.

Discussion

Monosodium Glutamate (MSG), locally known as "maggi" is one of the world's most widely used food additives. It used in modern nutrition worldwide as a flavor enhancer (Ikeda, 2002). MSG is widely used in Sudan by Sudanese families and recently it becomes very popular due to its availability and low price and especially under the harsh economic situation of the population. The use of maggi is more noted in rural areas either to replace meat or to give a good taste to the meal. In these areas, diseases like renal failure began to spread and researchers link this with their consumption of some unhealthy substances in food for long times. The toxic effects of MSG have been shown in numerous animal studies. Several studies in animals have shown that MSG is toxic to the various organs such as the liver, brain, thymus, and kidneys. Accordingly, the present study was performed to evaluate the toxic effect of monosodium glutamate on liver functions, Kidney functions, haematological parameters and histopathology in Wister rats.

The present study showed significant change in mean body weight of both treated groups (low and high doses) in comparison with the control group. The same result was reached by Inuwa *et al.*, (2011). It was found that exposure of rats to MSG at neonatal stage can severely damage their hypothalamic nuclei, which results in increased body weight, fat deposition as shown in previous studies (Nakagawa *et al*., 2000). Tawfik and Al-Badr (2012) also reported similar results with MSG-treated rats (0.6 and 1.6 mg/g body weight) for 2 weeks. The two authors reported a significant increase in the body weight along with relative weight of liver and kidney.

There is a significant change in haematological parameters; Hb concentration, RBCs, WBCs, Lymphocytes and Neutrophils of both treated groups when compared with control group and these finding were in agreement with a previous research by Ashaolu *et al.*, (2011). While the changes observed in MCH, MCHC, MCV showed in both treated groups when compared with control group our study disagreed with Ashaolu *et al.*, who reported that the change in these parameters' indicative of an anemic condition in the treated animals (Salisu *et al*., 2018).

The effect of MSG consumption in liver and kidney were probably contributed to alterations in activity of the liver enzymes (ALT, AST and ALP), total protein, urea, and creatinine the treated groups. The present study showed that, there is no significant change in mean of albumin concentration of both treated groups in compared with control group ($P > 0.05$) as previously shown by Oyetunji, (2013).

As liver was involved in detoxification and metabolism, so it may be directly affected by toxic chemicals or their metabolites, for example, MSG. According to Onyema *et al*., (2006), rats treated with MSG (0.6 mg/g body weight) for 10 days start to develop symptoms of liver damage. Similarly, MSG administration also elevated the activities of alanine aminotransferase (ALT), aspartate amino transferase (AST), and γ-glutamyl transferase (GGT) in serum. It has been confirmed that the damage to the liver caused by the production of reactive oxygen species (ROS). The liver depicted cytoplasmic fatty vacuolation of centrilobular hepatocytes and isolated cell necrosis.

The study here also shown that MSG induced many histological alterations in the kidneys of the tested including dilatation of renal tubules and epithelial cell degeneration or necrosis of the renal convoluted tubules of the glomeruli. These symptoms were confirmed by many previous studies e. g. Shilpi *et al*., (2014). Published data indicate that renal fibrosis is associated with the chronic consumption of MSG (Sharma *et al*., 2013), and oxidative stress is the main cause of kidney injury (Sharma *et al*., 2014). Decreased levels of major anti-oxidant enzymes and increased lipid peroxidation have been demonstrated in the

kidneys of chronic MSG-exposed rats (Paul *et al*., 2012; Thomas *et al*., 2009). Also, high doses of glutamate have been shown to induce significant toxicity in renal culture cells (Leung *et al*., 2008).

In addition, the present study showed infiltration of lymphocytes in the intestinal lamina propria and this result is in agreement with previous study of Ewek and Omlniabohs, (2007).

Conclusions

- Monosodium glutamate (MSG) is one of the world's most widely used food additives which enhances the food flavor.
- During the last decade it became apparent that the chronic intake of MSG has potential effects on the peripheral organs.
- This study concluded that MSG treatment might impair hepatic and renal functions and cause damage to liver and kidney.
- Based on these finding, it is recommended that individuals should restrict their dietary intake of foods containing this flavor enhancer.

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