POTENTIAL SUBCHRONIC TOXICITY OF MONOSODIUM GLUTAMATE (MSG) IN *Mus musculus* (Albino mice)

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Abstract: This study evaluated the sub-chronic toxicity of Monosodium Glutamate (MSG), a widely used flavour enhancer, in *Mus musculus* (albino mice). Twenty (20) male mice between 24–30 g were used in this study and were divided into four groups of five mice each. Groups A, B, and C were orally administered 100 mg kg^{-1}, 200 mg kg^{-1}, and 400 mg kg^{-1} of MSG for 42 days, while group D received distilled water (control). After the treatment period, the animals were euthanized to collect blood and internal organs for hematologic, biochemical, and bone marrow assays. Body weight of mice showed significant, dose-dependent increase across treatments, with significant increase in 100 mg kg^{-1} and 200 mg kg^{-1}. Hematologic parameters revealed significant increase in mean corpuscular haemoglobin concentration (MCHC) at 400 mg kg^{-1}, Red Cell Distribution With-Standard Deciatin in Femtoliters (RDW-SD FL) at 100 mg kg^{-1}, and platelet levels across all treatments compared to control. Biochemical profile indicated significant differences ($p<0.05$) in aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and creatine levels between treatments and control. Micronucleus assay revealed no significant differences ($p>0.05$) between treatment and control. The significant weight gain in MSG treated groups suggests hypothalamic effects on appetite and fat deposition. Significant increases in MCHC, RDW-SD FL, and platelet suggest potential anemic conditions and pro-inflammatory responses. Biochemical assay indicated improved liver function in MSG-treated mice, with decreased levels of AST, ALT, and ALP. Increased creatine levels may imply renal stress. Therefore, prolonged MSG administration at these doses, portends toxicity in body weight, kidney and hematological profiles.

Keywords: Monosodium Glutamate, Toxicity, Haematology, Liver Enzymes, Bone marrow assay

Introduction

Monosodium glutamate (MSG) is a popular flavour enhancer that is frequently added to a wide range of foods, such as canned and processed foods, homemade meals, and commercially prepared meals (Urcar-Gelen *et al.,* 2024). It is second only to table salt in terms of its popularity and used in many countries around the world (Afolabi and Olagoke, 2020). MSG, which is derived from glutamate, a non-essential amino acid, was identified several years ago as the fifth taste, known as umami, in addition to the existing four tastes of sour, bitter, salty, and sweet (Urcar-Gelen *et al.,* 2024). Its taste is regulated by glutamate receptors (T1R1 + T1R3) present in the taste buds, and gastrointestinal tract (El-Gendy *et al.,* 2023). The molecular mass of this compound is 169.11g mol^{-1}, and its chemical formula is $C_5H_8NNaO_4$ (Kayode *et al.,* 2023). It contains an alpha carbon atom that is bonded to both an amino ($-NH_2$) group and a carboxylic (-COOH) group (Kayode *et al.,* 2023).

MSG occurs naturally in a variety of foods including seaweed, tomatoes, shellfish, anchovies, cheeses, and vegetables (Kayode *et al.,* 2023). Additionally, MSG is found in numerous other common foods such as potatoes, eggs, cow milk, garlic, onions, almonds, and walnuts (Kayode *et al.,* 2023). Commercially, MSG is produced by fermenting molasses and other substrates suitable for the growth of the bacterium *Clostridium glutamicum* (Akanya *et al.,* 2015). Because they are biotin auxotrophs, these bacteria require biotin, or vitamin B7, as a cofactor (Ahmad-Hussin *et al.,* 2016). Among the molasses used for production are sugarcane and starch hydrolysates obtained from cassava or maize (Airaodion, 2019). Salts of ammonia and ammonium are added as a source of nitrogen, and additional nutrients and vitamins are added to complete the process (Airaodion *et al.,* 2019). In Nigeria, MSG is a vital component in many seasoning cubes, which are extensively utilized to enhance food flavors (Airaodion *et al.,* 2019). These seasoning cubes are widely available in street shops, markets, and supermarkets nationwide (Airaodion *et al.,* 2019).

The toxicity and safety of monosodium glutamate have been a topic of debate in recent years. This stems from reports of adverse reactions in individuals after consuming foods containing MSG (Shosha *et al.,* 2023). Numerous studies, particularly those conducted on animals, have confirmed the potential negative effects of MSG (El-Gendy *et al.,* 2023). These studies have shown that when MSG is continuously consumed in increased doses, it can be toxic and is associated with various adverse side effects (Airaodion *et al.,* 2019). In this context, it has been reported that MSG consumption can lead to symptoms such as an increase in insulin levels, headaches, and a rise in blood pressure (Mortensen *et al.,* 2017). Additionally, excessive long-term MSG consumption has been linked to metabolic syndrome and obesity (Nabi *et al.,* 2022). This is due to its effect on energy balance (Banerjee *et al.,* 2021). MSG increases food consumption by disrupting the hypothalamic signaling cascade that controls appetite and energy expenditure with leptin (Banerjee *et al.,* 2021). This disturbance may impair the ability to control hunger and fullness, causing overeating and obesity (Banerjee *et al.,* 2021).

Furthermore, MSG consumption has been connected to diseases like fibrosis, muscle atrophy, cardiac arrhythmias, oxidative stress, kidney tissue toxicity, neurotoxicity, hepatotoxicity, and behavioural disorders (Airaodion *et al.,* 2019).

Given the increasing concerns about the health risks associated with MSG, this study aimed to monitor and

analyze the sub-chronic toxic effects that MSG may have on *Mus musculus* over an extended period.

Materials and Methods

Experimental Animals

Twenty male mice (*Mus musculus*) between 24-30g were procured from the Nigerian Institute of Medical Research (NIMR) for the study. The animals were housed in plastic cages with wood shavings as bedding. They were kept at room temperature and fed with pellets and water *ad libitum*. The animals were allowed to acclimate for 7 days at the Botanical Gardens of the Faculty of Science, University of Lagos, before bioactivity. The animals were kept in a cycle of 12 hours of light and 12 hours of darkness, at 22±1°C temperature and 55±5% relative humidity. The mice were kept in well-ventilated cages with iron mesh covers and wood shaving. They were randomly divided into four equal groups, of five mice per group. The body weight of each group was recorded before the commencement of treatment and weekly. After the withdrawal of the treatment, the animals fasted overnight and were subsequently sacrificed under light ether anesthesia on the next day.

The study conformed to the requirements of 21 CFR 58: US FDA Good Laboratory Practices (GLP) Standards, 1987, and OECD Principles of GLP, 1997 (Bauter and Mendes, 2018).

Study Design

Groups A, B, C were administered 100 mg kg^{-1}, 200 mg kg^{-1}, and 400 mg kg^{-1}, respectively. The fourth group served as the control. They were orally administered the aqueous concentrates of MSG daily for six weeks. The weight of the mice was recorded weekly.

Collection of Blood and Organs

At the expiration of six weeks, all animals were sacrificed through jugular puncture. The blood samples of the mice were collected into labeled bottles of Ethylenediaminetetraacetic acid (EDTA) and Heparin for haematologic and biochemical analysis. The collected blood was centrifuged. The serum (Supernatant) was isolated and stored until it was analyzed. The biochemical and hematological analysis were carried out using standard assay kits from Randox Chemicals, UK, using Bayern instruments.

Bone Marrow Assay

According to the method described by (Oloyede *et al.*, 2020), bone marrow was prepared for micronucleus analysis. After sacrificing the animals, each individual's femur was removed, and bone marrow was purged from the bones using Foetal Bovine Serum (Germany: Sigma-Aldrich Chemie GmbH). The cells were centrifuged at 2000 rpm for 5 minutes, and May-Grunwald and Giemsa stains were applied to the transparencies. Micronuclei in polychromatic erythrocytes (MNPCE) were measured in at least 1000 cells/animal. PCEs (bluish-purple) are distinguished from normochromic erythrocytes (pinkish-orange) based on their differential staining and relative size.

Statistical Analysis

The data were subjected to a sample T-Test to determine the statistical significance of the difference between the two means of various parameters between the control and experimental groups. To get the P-value, a t-test in Microsoft Excel was utilized. A significant level of less than 0.05 was defined and considered significant.

Ethical approval

The use of albino mice for this project was authorized by the ethical committee of the College of Medicine University of Lagos (CMULHREC No. CMUL/ACURECA01/21/803).

RESULTS

The body weight as shown in Table 1 indicated a significant ($p<0.05$) dose-dependent increase in weight across the three doses. A significant increase was observed in the 5th and 6th week among the 100 mg kg^{-1} group, while there was a phenomenal significant increase in the group that received 200 mg kg^{-1} MSG dose throughout treatment. In the 400 mg kg^{-1} group, a significant increase was only observed in the 5th and 6th weeks although there was an insignificant increase in body weight from week 1 to week 4.

Table 1: Body weight of mice during exposure to MSG for 42 days

Treatment	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Control	25.72±0.47	25.0±0.65	26.32±1.11	27.48±0.72	25.76±1.87	26.56±1.51
100 mg kg^{-1}	27.7±0.75	26.48±3.92	30.04±2.04	30.92±1.99	$31.24±0.72^{b}$	$32.73±0.65^{b}$
200 mg kg^{-1}	$29.68±0.58^{a}$	$29.78±0.7^{a}$	$30.9±0.54^{b}$	$32.14±0.98^{b}$	$37.09±0.61^{c}$	$33.34±0.63^{b}$
400 mg kg^{-1}	31.08±0.52	32.18±1.51	31.49±0.56	32.34±0.69	$34.02±0.44^{b}$	$35.42±0.55^{b}$

Values are presented as mean ± SEM. Where n=5, value a = $p<0.05$, b=$p<0.01$, c=$p<0.001$.

Hematologic Profile of mice administered MSG

In the haematologic parameters evaluated (Table 2), there was no significant ($p>0.05$) difference between the means of white blood cells (WBC), red blood cells (RBC), hemoglobin (HgB), hematocrit (HCT), mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) between the treatments and the control ($p> 0.05$) of the male albino mice. However, the means of the mean corpuscular hemoglobin concentration (MCHC) of the 400 mg kg^{-1} albino, the mean of the RDW –SD FL in the 100 mg kg^{-1} treatment group, and all the treatment groups of the platelet level was significantly higher compared to the control.

Table 2: Hematology profile of the treatment groups and the control

Hematology profile	400 mg kg^{-1}	200 mg kg^{-1}	100 mg kg^{-1}	Control
WBC x 10^9/L	3.36 ±0.41	3.82±0.66	3.74±0.52	4.12±0.53
RBC x 10^{12}/L	7.88±0.44	9.51±0.21	7.57±0.74	8.82±0.28
HGB g/l	134.20±2.22	136.60±2.11	119.80±8.49	124.00±4.27
HCT g/l	0.40±0.03	0.48±0.01	0.41±0.04	0.46±0.01
MCV FL	50.06±1.37	50.48±0.47	54.84±0.47	51.82±1.04
MCH Pg	17.24±0.97	14.36±0.27	16.26±0.84	14.06±0.14
MCHC g/l	346.20±24.57^b	285.20±7.50	297.40±20.13	271.60±7.39
PLT * 10^9/L	625.20±51.35^c	500.80±59.24^b	709.40±92.15^c	430.00±57.01
RDW –SD FL	42.20±0.92	42.48±0.74	117.76±75.57^b	42.32±1.07
RDW-CV %	29.82±0.99	27.48±0.49	27.08±0.81	25.88±0.70
PDW FL	9.62±0.28	9.22±0.31	9.72±0.32	9.54±0.34
MPV FL	8.38±0.31	9.06±0.42	8.48±0.27	8.52±0.24
P-LCR %	9.38±0.37	9.06±0.28	8.56±0.17	7.96±0.32
PCR %	0.47±0.08	0.64±0.06	0.57±0.06	0.47±0.05
NEUT x 10^9/L	1.94±0.22	0.76±0.14	0.91±0.24	0.77±0.11
LYMPH x 10^9/L	1.94±0.32	2.46±0.49	2.13±0.24	2.56±0.40
MONO x 10^9/L	0.05±0.02	0.08±0.03	0.08±0.01	0.17±0.09
BOS x 10^9/L	0.12±0.06	0.11±0.07	0.17±0.09	0.20±0.06
BAS x 10^9/L	0.31±0.07	0.42±0.09	0.45±0.07	0.41±0.07
NBUT %	28.38±5.80	20.46±1.78	22.86±3.90	19.06±2.32
LYMPH %	57.54±4.58	62.52±1.33	2.42±0.44	3.88±2.08
MONO %	1.40±0.62	2.56±1.33	2.42±0.44	3.88±2.08
EO %	3.46±1.67	3.14±1.60	4.06±2.18	5.56±1.97
BAS %	9.22±1.60	11.32±1.59	12.78±2.01	10.00±1.41
IG x 10^9/L	0.05±0.03	0.05±0.03	0.07±0.03	0.09±0.03
IG %	1.44±0.84	1.44±0.63	1.88±0.77	2.40±0.88

Key: Values are mean ± SEM. Where N=5 value a =<0.05, b=<0.01, c=<0.001.

Biochemical Assay of the liver of the Treated Mice

The biochemical assay for the liver of the treated mice as shown in Tables 3 revealed a significant difference between 400 mg kg^{-1} and 200 mg kg^{-1} in the AST parameter, between the 400 mg kg^{-1} and 100 mg kg^{-1} in the AST, ALT and the ALP parameters and between the 400 mg kg^{-1} against the control in AST and the ALT parameters. Table 3 also showed a significant difference between the 200 mg kg^{-1}and 100 mg kg^{-1} in the AST parameter, between the 200 mg kg^{-1} and the control in the AST, CRT and the ALT parameters. Significant differences were also observed between the 100 mg kg^{-1} and the control in the UREA, ALT and CRT parameters. There is no significant increase in the ALB values obtained from the biochemical assay of the liver of the mice at all the treatment groups when compared to the control

Table 3: Biochemical assay of the treatments and the control of the liver of the mice

Biochemical assay	400 mg kg^{-1}	200 mg kg^{-1}	100 mg kg^{-1}	Control
AST (U/L)	43.40±3.01^b	28.83±2.76^b	67.09±7.60	79.94±12.84
ALT (U/L)	15.83±3.56^a	11.78±1.15^b	10.44±0.85^c	24.89±4.77
ALP (U/L)	17.50±7.50^a	22.06±10.00	66.00±29.00	53.50±39.50
UREA (mg/dl)	20.50±4.50	23.00±5.00	15.50±0.50^c	21.00±1.00
CRT (mg/dl)	0.30±0.08	0.40±0.01^c	0.36±0.03^a	0.28±0.03
ALB (g/L)	25.00±5.00	21.00±1.00	30.50±9.50	24.50±2.50

Key: Values are mean ± SEM. Where N=5 value a =<0.05, b=<0.01, c=<0.001.

Erythrocytes nuclear morphological abnormalities (ENMAs)

The cells with erythrocytes nuclear morphological abnormalities (ENMAs) present in the bone marrow in the treated mice experimental groups and the control were counted and evaluated. The letters ABC and D were used to represent 400 mg kg^{-1}, 200 mg kg^{-1}, 100 mg kg^{-1} and the control groups respectively (Table 5). The student's T-test showed that there is no significant difference in the values obtained from cells with erythrocytes nuclear morphological abnormalities (ENMAs) between the treatment groups when compared to the control.

Table 5: Erythrocytes nuclear morphological abnormalities (ENMAs) cell count of treatment and Control groups

PCO	400 mg kg^{-1}	200 mg kg^{-1}	100 mg kg^{-1}	Control
Kidney-shaped nucleus	1.00±0.00	1.00±0.00	4.00±0.95	1.00±1.67
Normal nucleus	366.00±265.50	775.00±101.50	419.00±61.57	402.00±105.00
Segmented Nucleus	1.00±0.00	1.00±0.00	5.00±2.50	1.00±0.00
Blebbed, Lobed or Notched Nucleus (BLNN)	3.00±0.95	1.00±00	5.00±2.20	2.00±2.00
Binucleated	17.00±4.40	11.00±6.50	20.00±2.30	16.00±7.30
Micronucleus	7.00±0.50	3.00±1.85	11.00±1.91	3.00±2.00
Vacuolated Nucleus	55.00±37.70	40.00±7.00	125.00±28.31	38.00±14.20
Polymorphic nucleus	1.00±0.00	1.00±0.00	5.00±2.40	3.00±0.95

Key: Values are mean ± SEM. Where N=5 value a =<0.05, b=<0.01, c=<0.01

Micronucleus Assay

The micronucleus assay of the bone marrow showing the erythrocyte cells identified in the bone marrow of the treatment and control mice is shown in Plate 1A-D

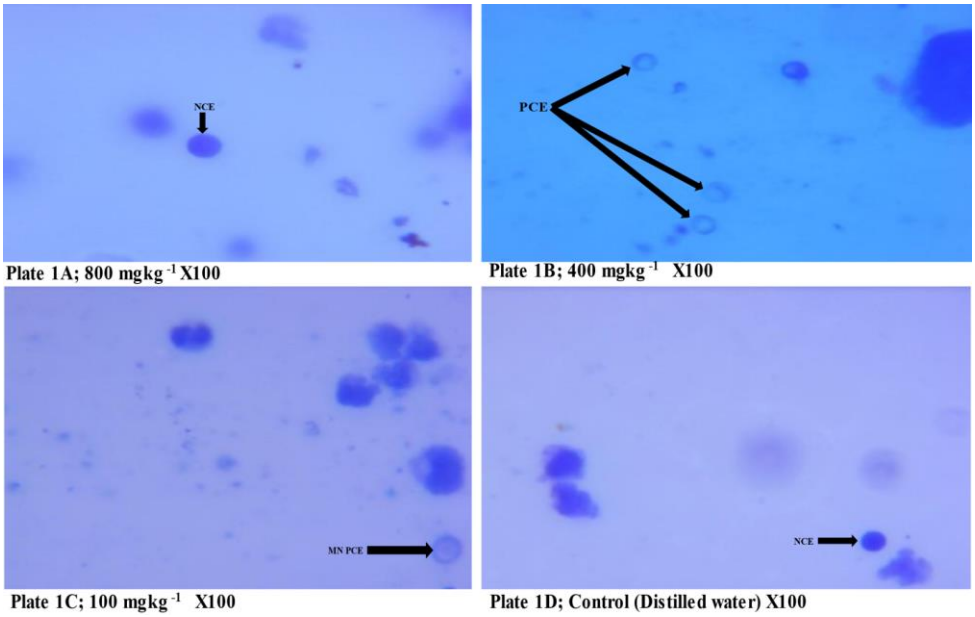

Plate 1A; 800 mgkg $^{-1}$ X100 Plate 1B; 400 mgkg $^{-1}$ X100

Plate 1C; 100 mgkg $^{-1}$ X100 Plate 1D; Control (Distilled water) X100

Plate 1A showed the presence of normochromatic erythroytes (NCE) - mature RBC that lacks RNA. **Plate 1B** showed the presence of Polychromatic erythrocyte (PCE), an immature RBC that contains RNA. **Plate 1C** revealed the presence of Polychromatic Erythrocyte (PCE), immature red blood cell that contains RNA and immature Micronucleated Polychromatic Erythrocyte (MN PCE). **Plate 1D** showed the presence of Normochromatic Erythrocytes (NCE) - mature RBC that lacks RNA.

Discussion

Body weight is a crucial factor in evaluating the toxicological effects of treatments, such as pharmaceuticals, extracts, and substances (Ajayi *et al.,* 2019). Weight fluctuations can act as initial and crucial indicators of toxicity (Ajayi *et al.,* 2019). The observed effects of MSG on body weight gain in our study is consistent with the results obtained by Adam *et al.*, (2019), who reported that the administration of MSG has detrimental consequences on the hypothalamic arcuate nucleus, leading to alterations in appetite control, increased feed consumption, fat deposition, and ultimately, an increase in body weight. Increased body weight is a major contributing factor to the development of several health conditions including metabolic syndrome, myocardial infarction, stroke, fatty liver disease, type 2 diabetes mellitus, and hypertension (Blüher, 2019). Therefore increased body weight caused by MSG in this study may be a sign of early toxicity. Hematological variables have been utilized recently to assess the toxicity or sublethal concentration of substances, medications, and environmental contaminants in humans and animals (Dhembare and Gaikwad, 2017). The insignificant differences between the hematologic parameters in the treatment and the control, such as white blood cells (WBC), red blood cells (RBC), hemoglobin (HgB), hematocrit (HCT), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH), suggest that MSG does not significantly impact these specific aspects of blood health (Akanya *et al.,* 2015). This observation aligns with the results reported by Akanya *et al.,* (2015) where they noted that the administration of MSG did not cause significant alterations in PCV, RBC count, and WBC levels in adult Wistar albino rats. However, the significant increases observed in specific parameters such as, the mean

corpuscular hemoglobin concentration (MCHC) in the 400 mg kg^{-1} treatment group, the mean of the RDW-SD FL in 100 mg kg^{-1} group, and the platelet levels across all treatment groups suggest a vital impact of MSG on hematology (Doig and Zhang, 2017). The increased MCHC at the 400 mg kg^{-1} MSG dosage may indicate a change in the shape of the RBCs, which could result in spherocytosis, an indication of anemia (Doig and Zhang, 2017). Increased RDW-SD FL in 100 mg kg^{-1} suggest that this dosage might lead to greater heterogeneity in the size of RBCs, a condition known as anisocytosis (Doig and Zhang, 2017).

Platelets play an important role in many body functions, such as inflammation, wound healing, and immunological response (Badr and Algefare, 2019). The significant increase in platelet counts of all treatment groups in comparison with the control may connote a pro-thrombotic or pro-inflammatory reaction probably induced by MSG (Badr and Algefare, 2019). Elevated platelet levels could imply that MSG triggers inflammatory processes, as platelets are essential for inflammation (Badr and Algefare, 2019).

Assessing the toxicity of substances depends on evaluating the activities of marker enzymes, which are essential biological indicators of liver health and potential damage (Oloyede *et al.,* 2021). This aspect was predicated specifically on three key liver enzymes: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP). Measuring the levels of these enzymes allows us to obtain reliable indicators of liver injury, which is vital for understanding the effects of prolonged MSG exposure on liver function (Oloyede *et al.*, 2021). The decreased AST levels at 200 mg kg^{-1} and 400 mg kg^{-1} may imply that MSG did not cause injury to the liver (Akanya *et al.*, 2015). AST is commonly used as a biomarker for liver damage, and a decrease in its levels typically signifies an improvement in liver function or a decrease in hepatocellular damage (Akanya *et al.,* 2015).

The significantly reduced levels of ALT compared to the control suggest that MSG did not alter the physiognomy of the liver (Kumar *et al.,* 2015). ALT is another crucial biomarker for liver health, often indicative of liver injury when elevated (Kumar *et al.,* 2015). Its reduction implies that there was decreased hepatocellular injury after prolonged intake (Kumar *et al.,* 2015). Furthermore, the significantly reduced ALP at 400 mg kg^{-1} may infer that MSG at the doses administered was not toxic to the liver (Akanya *et al.,* 2015). ALP is an enzyme linked to various liver and bone diseases, and its reduction suggests reduced negative impacts on liver function (Akanya *et al.,* 2015).

Various studies in rats have produced contradictory findings regarding the connection between liver biomarker levels and the consumption of MSG. According to Masre *et al.* (2019), *Sprague-Dawley* rats administered MSG displayed elevated levels of AST and ALT enzymes, suggesting potential liver tissue damage. Additionally, experiments by Ayanda *et al.* showed an increased level of ALP enzymes in mice treated with MSG, indicating damage due to cytotoxicity. Our study's findings on liver biomarkers contribute to the ongoing discussion about the safety of MSG and highlight the importance of considering factors like dosage, species variations, and individual differences when conducting toxicological assessments (Naiz *et al.,* 2018).

Lack of significant difference in albumin values between the control group, and the MSG treatments may indicate that there was no significant suppression of hepatic synthesis (Akanya *et al.,* 2015). Biomarkers such as creatinine and urea are crucial for detecting kidney injury as they reflect the organ's capacity to filter and remove waste from the body (Oloyede *et al.,* 2021). In our study, the significant increase in creatinine levels at 100 mg kg^{-1} and 200 mg kg^{-1} treatment may suggest that MSG, at these doses, imposes kidney stress (Thoalffakar *et al.,* 2021). The underlying cause for this stress could be a shift in the tubular reabsorption threshold (Thoalffakar *et al.,* 2021).

The micronucleus (MN) is a biomarker that can indicate chromosomal damage, particularly observed in young, recently formed red blood cells (Oloyede *et al.,* 2020). This damage occurs when chromosomal fragments are not properly incorporated into the daughter nuclei during the mitotic process of erythropoietic blast cells (Oloyede *et al.,* 2020). Absence of significant differences of treatment-related changes in MN frequencies, despite their visual observation on the slides, indicates that MSG at these treatment doses does not raise the risk of genotoxicity (Oloyede *et al.,* 2020). Furthermore, the lack of significant difference in the presence of nuclear morphological abnormalities in erythrocytes (ENMAs) among all the mice groups that were administered MSG suggests that subchronic exposure to MSG does not lead to any significant or observable changes in the nuclear structure of erythrocytes in mice (Shahjahan *et al.,* 2020).

Conclusion

The administration of MSG leads to an increase in body weight and changes in specific hematological parameters, suggesting possible anemia and inflammation. Despite these findings, MSG exposure decreased liver enzymes (AST, ALT, ALP), suggesting less hepatocellular damage. At the doses tested, MSG did not significantly increase chromosomal damage in red blood cells or alter their nuclear structure, suggesting a low risk of genotoxicity. However, elevated creatinine levels in some MSG-treated groups may indicate potential kidney stress. These findings contribute to the ongoing discussion about the safety of MSG and highlight the necessity for further research that spans a longer duration.

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Authors' contribution

The manuscript was written, and approved in collaboration with all authors.

Conflict of interests

All authors declare that there is no conflict of interest

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