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Research Article
Impact of Isoniazid on Metabolic Dysfunction, Toxicity and Lifespan in Long-Term Monosodium Glutamate-Treated Mice

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Abstract

Background and Objective: Monosodium glutamate (MSG) is a widely used flavor enhancer that has been associated with obesity and metabolic disturbances, as well as potential liver and kidney dysfunction. Considering the importance of these organs in metabolic regulation and detoxification, it is necessary to explore substances such as isoniazid (INH) that may alter or influence these effects. Therefore, this research focused on evaluating how INH affects metabolic parameters, toxicity indicators and the functional status of the liver and kidneys in MSG-exposed animals. **Materials and Methods:** A total of forty-eight male Swiss albino mice were arbitrarily assigned to six experimental groups: A saline-treated control group, a negative control group receiving isoniazid (INH, 100 mg/kg for 10 days), a positive control group administered monosodium glutamate (MSG, 4 mg/kg for 40 days) and three treatment groups receiving MSG (40 days) in combination with INH at concentrations of 25, 50 and 100 mg/kg, respectively for last 10 days. Animals from all groups were evaluated for metabolic alterations, clinical indicators of toxicity, survival outcomes and pointers of renal and hepatic dysfunction. Statistical investigation was accomplished employing one-way analysis of variance (ANOVA) along with Tukey's *post hoc* multiple comparison test and statistical implication labeled as $p<0.05$. **Results:** The findings verified that continuous MSG exposure significantly ($p<0.01$) amplified body weight, food and water intake, blood glucose, grimace scores, renal and hepatic biomarkers and mortality in mice, suggesting noticeable metabolic and systemic toxicity. Co-administration of INH produced a dose-dependent aggravation of MSG-induced adverse effects. Notably, INH at concentrations of 50 and 100 mg/kg significantly intensified ($p<0.01$) metabolic disturbances (except blood glucose levels) grimace scale scores and markers of kidney and liver dysfunction comparative to the MSG-only group. Furthermore, INH treatment raised mortality rates in MSG-exposed mice. **Conclusion:** The results reveal that INH can aggravate the adverse effects associated with chronic MSG exposure and increase the risk of complications. Further research is affirmed to validate these observations and to explain the exact impact of MSG on health outcomes, as well as its potential interactions with frequently used therapeutic agents.

Key words: Monosodium glutamate, metabolic defects, toxicity, isoniazid, mice

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

A wide range of food additives are routinely integrated into processed foods to improve sensory attributes, shelf stability, texture and visual appeal. Among these additives, monosodium glutamate (MSG) is greatly utilized as a flavor-enhancing agent due to its ability to intensify palatability and increase the commercial attractiveness of food products[1].

Monosodium glutamate (MSG) has been reported to add to weight gain and the development of obesity-related syndromes by altering energy homeostasis in humans[2]. In addition, experimental studies in animal models have associated MSG exposure with a choice of metabolic and neurobehavioral abnormalities[3]. Previous investigations have shown that MSG can induce structural and functional damage to the arcuate nucleus of the hypothalamus, thereby interrupting neuronal pathways involved in leptin and insulin signaling[4]. Furthermore, MSG administration has been linked to raised levels of inflammatory mediators and oxidative stress biomarkers, which are recognized contributors to cellular injury. These pathophysiological alterations may negatively affect normal organ function and impair endogenous repair mechanisms that defend against disease progression[5].

Tuberculosis (TB) remains a major infectious disease affecting populations across varied geographical regions worldwide. Epidemiological estimates indicate that the global occurrence of TB is approximately 134 cases per 100,000 individuals[6]. Such a high disease burden not only poses significant public health trials but also contributes substantially to the economic strain experienced by affected individuals and the healthcare systems accountable for diagnosis, treatment and disease control[6,7].

Isoniazid (INH) is a cornerstone of first-line antitubercular therapy and is widely employed in the treatment of patients diagnosed with tuberculosis. While generally effective, INH administration has been associated with numerous adverse effects, including peripheral neuropathy, cutaneous reactions, anemia and, in rare cases, systemic lupus erythematosus[8]. Although nephrotoxicity is uncommon, hepatotoxicity remains one of the most regularly reported complications associated with INH therapy[9].

Research has shown that prolonged exposure to specific chemicals including food additives can modulate the pharmacological effects of therapeutic drugs. MSG, commonly present in various food products, has the potential to change the efficacy and safety profile of several medications, including INH[10]. In such scenarios, both patients and healthcare providers may find it challenging to identify or predict the adverse interactions and complications that could arise from the combined impact of dietary chemicals like MSG and pharmacological agents such as INH[11,12].

Investigating the effects of chronic exposure to dietary chemicals such as MSG could provide significant insights into their potential impact on patient health and therapeutic outcomes[13]. Data from such studies may guide healthcare providers in selecting applicable medications and identifying clinical parameters that should be regularly monitored to ensure patient safety and heighten drug efficacy[14]. Accordingly, the current study was intended to assess the influence of MSG on metabolic modifications and general indicators of toxicity, while also assessing the modulatory properties of INH on renal and hepatic function markers in an experimental mouse model.

MATERIALS AND METHODS

Study area and duration: The study was conducted in the Research Laboratories of College of Pharmacy, Qassim University, Buraidah, Saudi Arabia as per the guidelines of good laboratory practice from June 2025 to January 2026.

Chemicals and drugs: Monosodium glutamate (MSG; AJI-NO-MOTO, Batch No. 1186, Foods Europe, France) was bought from a local market. Isoniazid (INH; Cat No. 375, Macleods Pharmaceutical Limited, India) was procured through a licensed supplier authorized by the institution, ensuring adherence to quality and safety standards. All other necessary reagents, including solvents and chemicals, were taken from the college's chemical storage facility. These substances were of analytical grade, appropriate for accurate and dependable experimental work.

Animals: A total of 48 adult male Swiss albino mice, approximately 9 weeks old and weighing between 18 and 25 g, were taken from the animal house of the College of Pharmacy at Qassim University, Kingdom of Saudi Arabia. The mice were randomly divided into six experimental groups, with six animals in every group. Ethical authorization for the use of animals was obtained from the Committee of Research Ethics under the Deanship of Graduate Studies and Scientific Research at Qassim University (Approval No. 25-48-02) preceding to the start of the experiments. All mice were maintained under controlled laboratory conditions, including a 12 hrs light/dark cycle, controlled temperature and moisture. They had unlimited access to standard pelleted feed and fresh

drinking water throughout the research. Furthermore, the animals were permitted a one-week acclimatization period to adjust to the laboratory environment before the initiation of drug administration.

Animal grouping and treatment protocol: Randomly selected mice were congregated as follows:

- **Group-A:** Control (Normal saline)
- **Group-B:** Negative control (Isoniazid-100 mg/kg, intraperitoneal (i.p) for 10 days)[15]
- **Group-C:** Positive control (MSG-4 mg/kg, oral for 40 days)[16]
- **Group-D:** Treatment-1: MSG+Low dose of INH (25 mg/kg, i.p for 10 days)
- **Group-E:** Treatment-2: MSG+Medial dose of INH (50 mg/kg, i.p for 10 days)[15]
- **Group-F:** Treatment-3: MSG+High dose of INH (100 mg/kg, i.p for 10 days)

A metabolic disorder was induced in experimental animals by orally administering MSG at a dosage of 4 mg per gram of body weight for 40 continuous days. The animals were then treated with isoniazid (INH) at different doses for 10 days, while MSG administration continued simultaneously throughout the INH treatment period. Animals that received only MSG for 40 days served as the positive control group, whereas those administered the maximum tested concentration of INH (100 mg/kg) for 10 days without MSG were designated as the negative control group[17].

Experimental parameters

Metabolic changes: Metabolic changes following the respective treatments were evaluated by monitoring body weight, water intake, food intake and blood glucose levels. Body weight was measured using a calibrated digital balance. Each mouse was gently isolated from its cage, sited individually in a pre-weighed container and weighed. The animals were instantly restored to their home enclosures and the container was cleaned between measurements to prevent cross-contamination. Weighing was carried out at the time each day throughout the study and all data were systematically recorded along with the mouse ID, date and corresponding experimental group[18].

Each mouse was housed separately with pre-weighed food and water. Food was calculated at the starting and finish of the observation period and any spillage was collected and included in the calculations. Water intake was monitored by weighing the bottles or assessing their volume at the same intervals. Daily food and water consumption for each mouse was determined by subtracting the remaining amount from the initial quantity and the results were recorded along with the mouse ID and date. All measurements were conducted at uniform times each day to minimize variability[19].

Blood glucose readings were estimated using a glucometer (LOT # 31205638; Accu-Chek, Roche International Ltd, Uruguay) in six hour fasting state of animals. Each mouse was gently restrained and a small drop of blood was amassed from the tail tip after sterilizing the area with alcohol. The blood drop was applied to the test strip and the glucose concentration was recorded. Measurements were performed at the same time each day to minimize diurnal variations and the mouse ID, date and glucose values were systematically documented[18].

Mouse grimace scale: Experimental animals were observed in a calm environment, either within their home cages or in a familiar observation area. Facial expressions were evaluated using the five standard Mouse Grimace Scale (MGS) action units: Orbital tightening, nose bulge, cheek bulge, ear position and whisker change. Assessments were conducted directly with every activity scored on a scale of 0 to 2 (0 = absent, 1 = moderate, 2 = severe) following established guidelines. Scores for each mouse were recorded along with the date and experimental condition, ensuring minimal handling and stress during evaluation[20].

Monitoring general signs of toxicity: Mice were observed each day for indices of toxicity, plus changes in behaviour, activity levels, posture, grooming habits, eye condition, skin appearance, fur quality and excretion patterns (faeces and urine). Any abnormalities, such as redness, swelling, lesions, diarrhoea, or changes in urination, were carefully noted. Observations were methodically recorded for each mouse in form of signs (- is normal, + is mild, ++ is moderate, +++ is severe), along with the date and corresponding experimental group, throughout the study period[21].

Kidney function test: Serum creatinine and blood urea nitrogen (BUN) were evaluated to estimate kidney function. Blood samples were amassed through retro-orbital bleeding under light ether anaesthesia. Serum was removed by centrifugation at 3000 rpm for 10 min and stored at -20°C until analysis. Levels of serum creatinine and BUN were established using commercially available assay kits (creatinine from MyBioSource, USA; LOT # 866213) and BUN from

MyBioSource, USA; LOT # 253149)) according to the manufacturer's instructions. Briefly, creatinine is first hydrolyzed to creatinine, which is then converted to sarcosine; sarcosine is subsequently oxidized to generate hydrogen peroxide. The hydrogen peroxide reacts with a chromogenic substrate to generate a colored product, with the strength of the color relative to the creatinine content. BUN was measured enzymatically through the conversion of urea to ammonia, which reacts to form a colorimetric product, with the intensity directly reflecting serum urea levels[22].

Liver function test: Serum Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) activities were calculated to evaluate liver function. Blood samples were amassed through retro-orbital flow of blood under light-ether anaesthesia. Serum was removed by centrifugation at 3000 rpm for 10 min and kept at -20°C until analysis. The ALT and AST activities were determined using commercially available assay kits (ALT from MyBioSource, USA; LOT # 421890) and AST from MyBioSource, USA; LOT # 085527) following the manufacturer's instructions. Briefly, ALT catalyzes the translation of alanine and α-ketoglutarate to pyruvate and glutamate, while AST catalyses the translation of aspartate and α-ketoglutarate to oxaloacetate and glutamate. These reactions are coupled to colorimetric or enzymatic assays and the rate of difference in optical density is directly relative to the enzyme activity in the serum[23].

Percentage survival rate: Experimental mice were monitored daily for mortality and the total of surviving animals in every group was recorded. Percentage survival was finalized by parting the numeral of surviving mice by the total number at the start of the study and multiplying by 100. All observations were systematically recorded along with the date and corresponding experimental group[21].

Data analysis: For statistical analysis, data from eight mice per experimental group were compiled. Results are represented as Mean±Standard Deviation (SD) and presented in figures. Statistical comparisons were accomplished using GraphPad Prism software. One-way Analysis of Variance (ANOVA) was employed along with Tukey's *post hoc* test to recognize significant distinctions between groups. Statistical implication was fixed at a p-value of less than 0.05, with $p<0.05$ considered significant, $p<0.01$ considered very significant and $p<0.001$ reflected highly significant[23]. The negative control group (INH alone at 100 mg/kg) and positive control group (MSG at 4 mg/g) were each related to the normal control group. Additionally, the treatment groups receiving MSG+INH were matched with the positive control group that received MSG alone.

RESULTS

Metabolic changes: The findings from the experiment implied that daily intake of MSG positively influenced body weight. From day 20 onwards, a substantial ($p<0.05$) rise in body weight was witnessed in experimental animals, which further raised on day 30 ($p<0.01$) and day 40 ($p<0.001$) when matched to the control group. Furthermore, when INH was administered to MSG-treated animals, a substantial enhancement in body weight was recorded at dosages of 50 mg/kg ($p<0.05$) and 100 mg/kg ($p<0.01$) compared with the MSG group. However, the lesser dose of INH (25 mg/kg) did not show a significant deviation in body weight. On contrary, the maximum tested concentration of INH (100 mg/kg) did not notably modified body weight in comparison with control group (Fig. 1a).

The study on food intake suggested that MSG-induced experimental animals displayed a considerable ($p<0.05$) enhancement in food intake from day 20 onwards in comparison with the control group. Among the three tested doses, INH at 50 mg/kg and 100 mg/kg significantly ($p<0.001$) declined food intake relative with the MSG-treated group (Fig. 1b). Similarly, water intake was found to be significantly improved in MSG-treated mice from day 20 onwards ($p<0.01$) in comparison with the control group. Treatment with INH at doses of 50 mg/kg and 100 mg/kg along with MSG considerably ($p<0.001$) diminished water intake (Fig. 1c).

Blood glucose estimation revealed that MSG induction markedly ($p<0.05$) raised blood glucose values after 20 days compared with control animals. INH administered at 100 mg/kg did not construct a variable distinction in blood glucose values compared with the control group. Furthermore, when all three doses of INH (25, 50 and 100 mg/kg) were administered along with MSG, none of the treatments displayed a significant alteration in blood glucose levels compared with MSG-treated animals (Fig. 1d).

Grimace scale: The mean scores for orbital tightening indicated that MSG administration for 20 days markedly ($p<0.01$) heightened the scores in comparison to control animals. The INH alone at 100 mg/kg did not markedly modify the scores relative with the control animals.

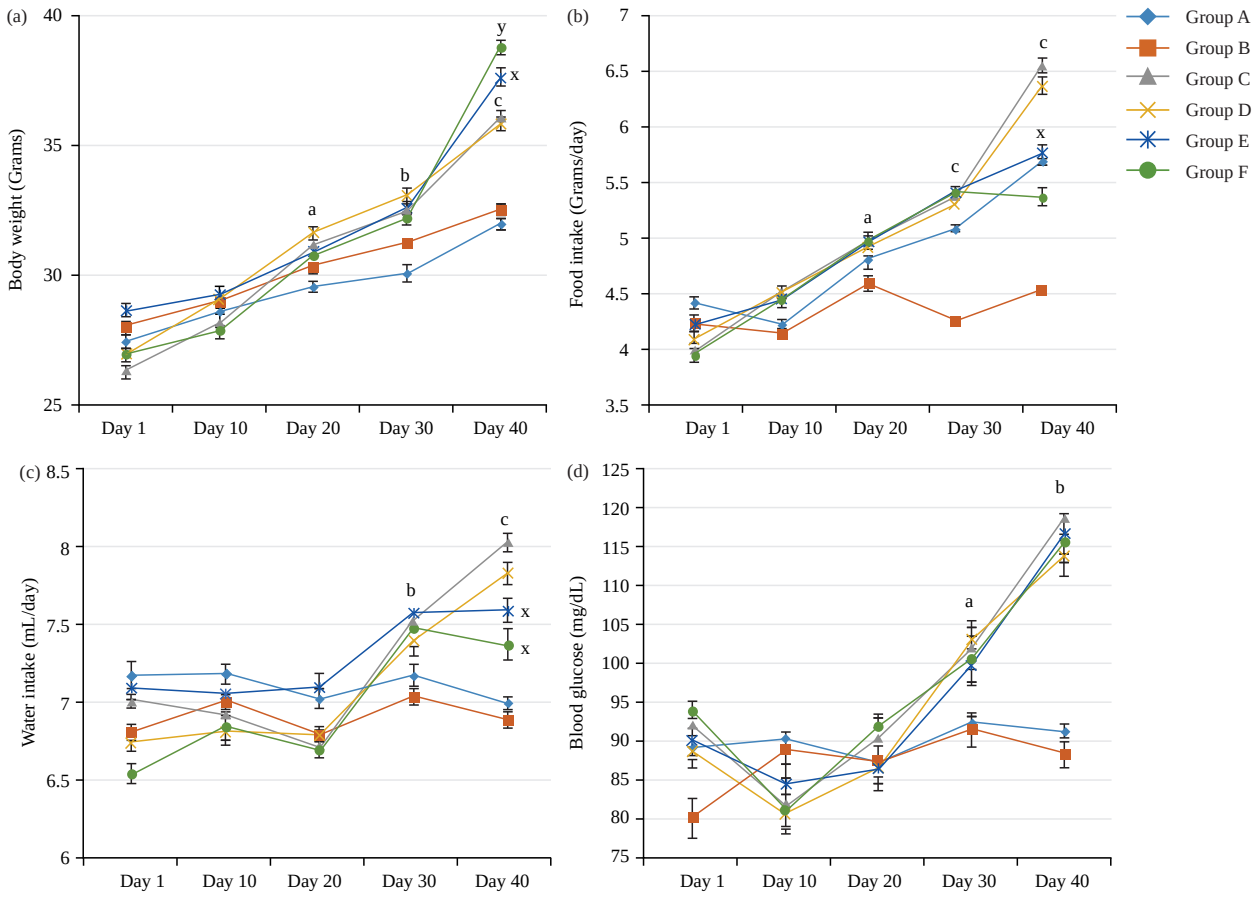

Fig. 1(a-d): Effect of INH on MSG-induced metabolic defects, (a) Body weight, (b) Food intake, (c) Water intake, (d) Blood glucose
Group A is control, Group B is INH (100 mg/kg), Group C is MSG (4 mg/kg), Group D is MSG+INH (25 mg/kg), Group E is MSG+INH (50 mg/kg), Group F is MSG+INH (100 mg/kg), N = 8. One-way ANOVA along with Tukey's test. Data is expressed as Mean±SD, $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$ Vs control group and $^{x}p<0.01$ Vs MSG group

Nevertheless, when INH at dosages of 50 and 100 mg/kg was given to MSG-induced animals, the orbital tightening scores were drastically ($p<0.01$) raised than those of the MSG data. The lower dose of INH (25 mg/kg) did not produce significant alterations in mean scores when tested along with MSG (Fig. 2a).

The data on nose/cheek flattening scores suggested that MSG induction markedly ($p<0.05$) increased the scores from day 20 onwards compared with the control mice. Moreover, INH at dosages of 50 mg/kg and 100 mg/kg, when given to MSG-treated mice, substantially ($p<0.001$) raised the scores relative with the MSG group (Fig. 2b). Similarly, the scores recorded for ear changes and whisker changes displayed a marked ($p<0.05$) heightened in MSG-treated mice beyond 20 days in comparison with the control animals. Furthermore, INH treated at concentrations of 50 and 100 mg/kg along with MSG further enhanced these scores for both ear and whisker changes compared with MSG-treated animals. In all these assessments, INH alone at 100 mg/kg did not produce any noticeable variation relative with the control group (Fig. 2c-d).

General toxicity: The general toxicity signs observed in the eyes suggested that MSG induction beyond 20 days produced noticeable changes, including eye dullness, pupil dilatation and ptosis. These signs were further increased when INH (50 and 100 mg/kg) was administered along with MSG. Regarding the skin, changes in hair color were observed beyond 30 days of MSG exposure. In addition, changes in skin texture were noted after 40 days of MSG induction in experimental animals. INH, particularly at the maximum tested amount (100 mg/kg), was found to exacerbate all these signs of skin toxicity shown in Table 1.

With respect to excretory parameters, MSG induction beyond 30 days resulted in marked variations in bowel color, loose stools and soiling of the perineum. Administration of INH at concentration of 50 and 100 mg/kg further enhanced these

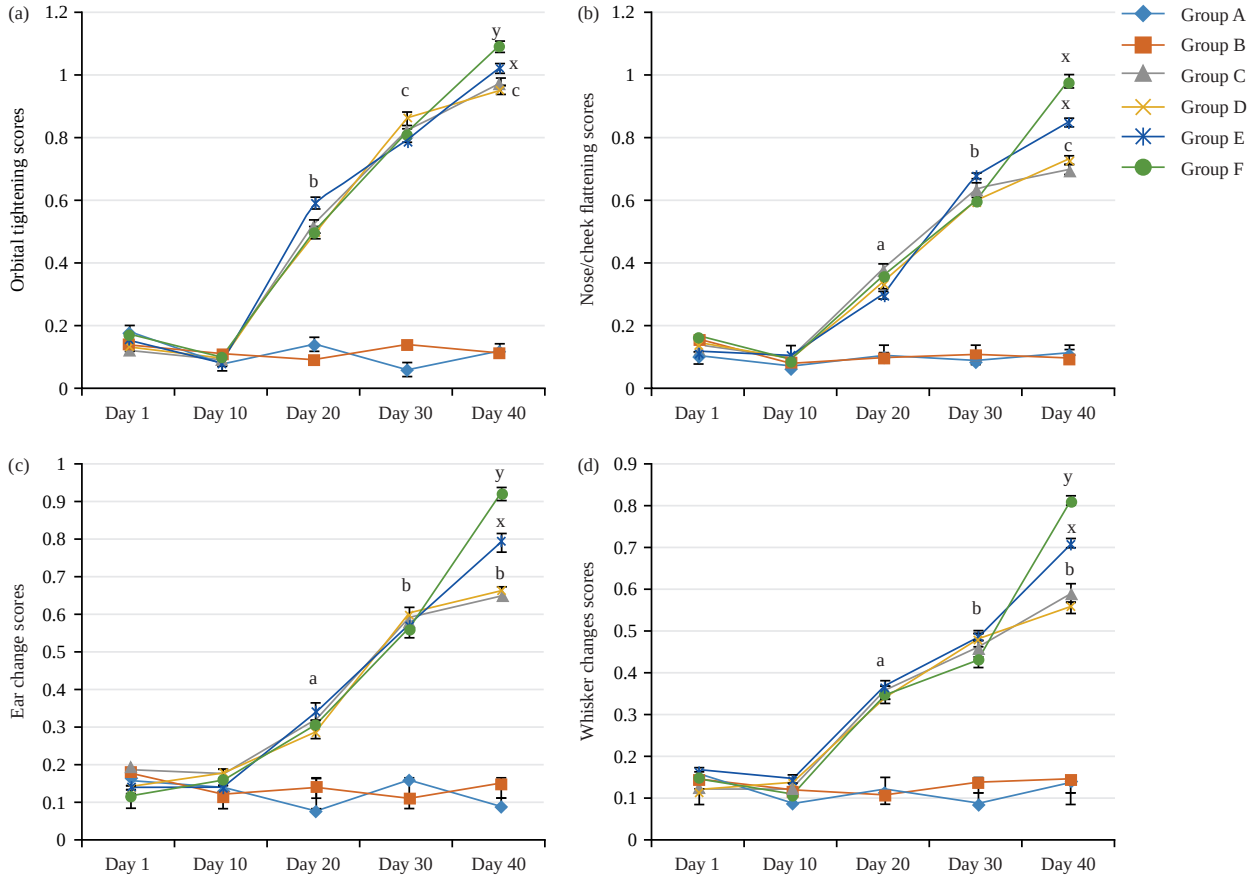

Fig. 2(a-d): Effect of INH on MSG-induced Grimace scores defects, (a) Orbital tightening, (b) Nose/cheek flattening, (c) Ear changes and (d) Whisker changes

Group A is control, Group B is INH (100 mg/kg), Group C is MSG (4 mg/kg), Group D is MSG+INH (25 mg/kg), Group E is MSG+INH (50 mg/kg), Group F is MSG+INH (100 mg/kg), N = 8. One-way ANOVA followed by Tukey's test. Data is expressed as Mean±SD, $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$ Vs control group: $^{x}p<0.05$ and $^{y}p<0.01$ Vs MSG group

signs in MSG-treated animals. Concerning respiratory and locomotor parameters, MSG induction led to breathing difficulties beyond 20 days of exposure, gait alterations at 40 days and abdominal distension beyond 30 days of induction. All these signs were found to be more noticeable when INH, especially at 100 mg/kg, was administered along with MSG in experimental animals.

Kidney and liver function tests: Serum creatinine and blood urea nitrogen (BUN) values were measured to estimate kidney function in experimental mice. The study observations indicated that MSG induction markedly ($p<0.05$) enhanced creatinine and BUN values beyond 20 days of exposure related with the control group. INH alone at 100 mg/kg and INH at 25 mg/kg administered with MSG did not significantly alter these parameters. However, administration of INH at concentration of 50 mg/kg and 100 mg/kg to MSG-induced animals ensued in a noteworthy ($p<0.05$) rise in creatinine and BUN levels in comparison with the MSG-treated group (Fig. 3a-b).

Hepatic function was analysed by measuring alanine transaminase (ALT) and aspartate aminotransferase (AST) concentrations. MSG induction beyond 20 days significantly ($p<0.05$) elevated these hepatic markers enzymes compared with the control group. INH administered at dosages of 50 and 100 mg/kg further escalated ALT and AST levels likened with the MSG group. INH alone at 100 mg/kg did not show a significant variation in hepatic enzyme values in control animals. Additionally, the lower dose of INH (25 mg/kg), when administered along with MSG, did not show any significant alteration in liver enzyme levels compared with MSG-treated animals (Fig. 3c-d).

Table 1: Effect of INH on MSG-induced general toxicity signs

	Eye														
	Eye dullness (Days)					Pupil dilatation (Days)					Ptosis (Days)				
Groupings	0	10	20	30	40	0	10	20	30	40	0	10	20	30	40
Group A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group C	-	-	+	+	++	-	-	-	+	+	-	-	+	+	++
Group D	-	-	+	+	++	-	-	-	+	+	-	-	+	+	++
Group E	-	-	+	+	+++	-	-	-	+	++	-	-	+	+	++
Group F	-	-	+	+	+++	-	-	-	+	++	-	-	+	+	+++
	Skin														
	Change in hair colour (Days)					Skin texture abnormality (Days)					Subcutaneous swelling (Days)				
Group A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group C	-	-	-	+	+	-	-	-	-	+	-	-	-	-	-
Group D	-	-	-	+	+	-	-	-	-	+	-	-	-	-	+
Group E	-	-	-	+	+	-	-	-	-	+	-	-	-	-	++
Group F	-	-	-	+	++	-	-	-	-	++	-	-	-	-	+++
	Excretion														
	Change in bowel color (Days)					Loose stools (Days)					Soiling of perineum (Days)				
Group A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group C	-	-	+	+	+	-	-	-	+	+	-	-	-	+	+
Group D	-	-	+	+	++	-	-	-	+	+	-	-	-	+	+
Group E	-	-	+	+	++	-	-	-	+	+	-	-	-	+	++
Group F	-	-	+	+	+++	-	-	-	+	++	-	-	-	+	++
	Others														
	Breathing difficulties (Days)					Gait alteration (Days)					Abdomen distension (Days)				
Group A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Group C	-	-	-	+	+	-	-	-	-	+	-	-	-	+	++
Group D	-	-	-	+	+	-	-	-	-	+	-	-	-	+	++
Group E	-	-	-	+	++	-	-	-	-	+	-	-	-	+	++
Group F	-	-	-	+	++	-	-	-	-	++	-	-	-	+	+++

Group A is control, Group B is INH (100 mg/kg), Group C is MSG (4 mg/kg), Group D is MSG+INH (25 mg/kg), Group E is MSG+INH (50 mg/kg), Group F is MSG+INH (100 mg/kg), N = 8, -: Indicates normal, +: Indicated mild, ++: Indicates moderate and +++: Indicates severe alteration

Percentage survival rate: The percentage survival rate data implied that MSG treatment was beyond 30 days and resulted in a mortality rate of 5%, which further increased to 10% after 40 days of exposure. INH alone at 100 mg/kg did not produce any mortality under normal conditions. However, when INH was administered along with MSG, an enhancement in mortality rate was detected. INH at 50 mg/kg induced 15% mortality in MSG-treated animals, which further increased to 25% when INH was experimented at 100 mg/kg (Fig. 4).

DISCUSSION

The findings of the current research displayed that chronic introduction to MSG negatively impacted metabolic parameters and elevated general toxicity indicators, mortality rates and markers of renal and hepatic dysfunction in mice. Furthermore, co-administration of INH in MSG-exposed animals intensified these adverse effects, indicating that prolonged MSG ingesting may potentiate the toxicological profile of INH.

The data of the work demonstrated that MSG exposure led to a marked rise in body weight in experimental animals. Previous research has indicated that MSG can induce harm to key brain regions accountable for regulating appetite, energy homeostasis and hormonal signaling[3]. Consistent with this, MSG-treated animals exhibited intensified food intake, a response that may be attributed to the umami taste of MSG, which augments food palatability, encourages larger portion sizes and promotes greater caloric consumption[4]. Additionally, activation of dopaminergic reward pathways, along with),

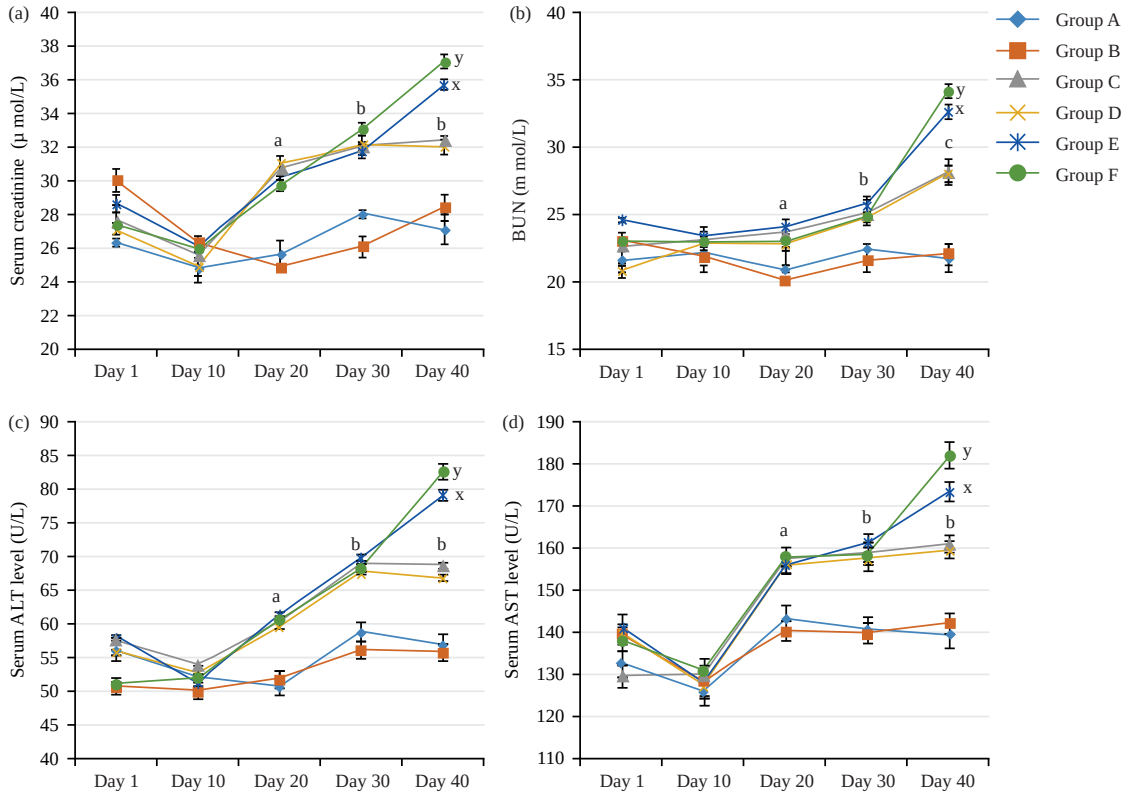

Fig. 3: Effect of INH on MSG-induced renal and liver dysfunctions, (a) Serum creatinine, (b) Blood urea nitrogen, (c) Serum ALT and (d) Serum AST

Group A is control, Group B is INH (100 mg/kg), Group C is MSG (4 mg/kg), Group D is MSG+INH (25 mg/kg), Group E is MSG+INH (50 mg/kg), Group F is MSG+INH (100 mg/kg), N = 8. One-way ANOVA followed by Tukey's test. Data is expressed as Mean±SD, $^{a}p<0.05$, $^{b}p<0.01$, $^{c}p<0.001$ Vs control group: $^{x}p<0.05$, $^{y}p<0.01$ Vs MSG group

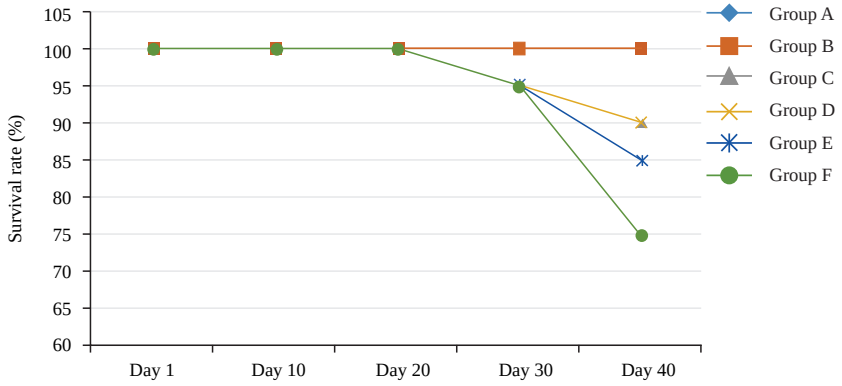

Fig. 4: Effect of INH on MSG-induced changes in survival rate, Group A is control, Group B is INH (100 mg/kg), Group C is MSG (4 mg/kg), Group D is MSG+INH (25 mg/kg), Group E is MSG+INH (50 mg/kg), Group F is MSG+INH (100 mg/kg), N = 8 and Data is expressed as percentage survival rate

repression of satiety signals mediated by hormones such as cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1 has been implicated in MSG-related hyperphagia. Such behavioral and neurochemical changes are identified contributors to obesity and weight gain in individuals with chronic MSG consumption[24].

Animals exposed to MSG also exhibited increased water intake. This effect is probable attributable to the sodium content of MSG, which elevates plasma osmolality and activates hypothalamic osmoreceptors, thereby stimulating thirst centers[5]. In addition, central actions of glutamate have been reported, with MSG potentially activating hypothalamic regions concerned in the regulation of fluid intake[25].

Our findings also revealed that MSG exposure resulted in significant rise of kidney function markers, including serum creatinine and blood urea nitrogen (BUN), together with hepatic enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Previous studies have showed that impaired kidney and liver function can lead to the accumulation of endogenous toxins, such as ammonia, bilirubin, bile acids, drugs and xenobiotics[22]. The buildup of these substances can stage the production of reactive oxygen species, contributing to oxidative stress[23]. Collectively, these pathological changes may underline the observed rises in grimace scores and the advent of general signs of toxicity in MSG-exposed experimental animals[20,22,23].

A key observation of the research is that co-administration of INH to MSG-exposed mice exacerbated metabolic irregularities and amplified indicators of general toxicity, including impairments in renal and hepatic function. Previous research has indicated that INH can induce renal damage through numerous mechanisms, including immune-mediated hypersensitivity reactions, immune complex-mediated glomerular damage, oxidative stress triggered by toxic metabolites and rhabdomyolysis-associated renal impairment[26].

Furthermore, hepatotoxicity induced by INH is well recognized. Its metabolites, including acetyl hydrazine and hydrazine, are known to produce reactive oxygen species, promote lipid peroxidation and upset mitochondrial function, jointly contributing to liver injury[27]. In addition, secondary mechanisms such as immune-mediated hepatic injury have also been reported to play a part in INH-associated hepatotoxicity[28].

Another notable outcome of the study was the impact on survival rates. Chronic exposure to MSG alone was associated with heightened mortality in experimental animals. While the maximum tested concentration of INH (100 mg/kg) did not cause mortality under normal conditions, its co-administration with MSG significantly raised the death rate, implying a synergistic effect that intensified the severity of toxic reactions[29].

The findings of the present study reveal that chronic exposure to MSG can prompt metabolic abnormalities and contribute to toxic manifestations, as well as impair the function of essential organs such as the kidney and liver. These metabolic disturbances may further worsen renal and hepatic dysfunction and conversely, organ impairments can intensify metabolic defects, creating a reciprocal pathological correlation. Notably, MSG appears to concurrently promote metabolic dysregulation and compromise renal and hepatic function. Although INH is known to cause adverse effects on its own, its administration in animals formerly exposed to MSG significantly potentiated these complications, including intensified toxicity and mortality.

Collectively, the results emphasize the importance of evaluating the effects of regularly used dietary additives, such as MSG, on overall health and highlight their potential to alter the adverse effects of conventional pharmacological agents like INH. However, it is noteworthy that these data are from experimental studies conducted in controlled animal models and may not be fully interpreted to human populations. Further research is warranted to justify these observations using diverse experimental models and to assess additional biomarkers that exhibit metabolic disturbances, systemic toxicity and renal and hepatic dysfunction. Such studies would help justify the broader relevance of MSG exposure and its potential connections with pharmacological agents like INH in humans.

CONCLUSION

The study revealed that chronic administration of MSG can induce metabolic disturbances, including raised body weight, food and water intake and elevated blood glucose values. Long-term MSG exposure was also linked with systemic toxicity, increased mortality and impairment of renal and hepatic function. Co-administration of INH further aggravated these adverse effects. The underlying mechanisms are likely multifactorial, involving neuroendocrine disruption, pancreatic β-cell damage, oxidative stress and inflammation. These findings provide prominent insights for both patients and healthcare providers regarding the potential long-term effects of MSG consumption and how such effects may be amplified when combined with conventional medicines like INH. Nevertheless, supplementary studies are obligatory to validate these observations, elucidate the precise mechanisms involved and evaluate the significance of these effects in both animal models and human populations.

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