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Research article

Metabolic effects of a submaximal dose of pink salt and monosodium glutamate in experimental rats

Thamer Abdullah Alharbi [a], Syed Imam Rabbani [b], Raha Orfali [c], Moneer E. Almadani [d], Fuzail Ahmad [e], Rafiulla Gilkaramenthi [f], Ebtesam Abdulrahman Jibreel [g], Mohammed Sharique Ahmed Quadri [h], Syed Mohammed Basheeruddin Asdaq [i,*]

[a] Clinical Pharmacist, Kingdom of Saudi Arabia
[b] Department of Pharmacology and Toxicology, College of Pharmacy, Qassim University, Buraydah, 51452, Kingdom of Saudi Arabia
[c] Department of Pharmacognosy, College of Pharmacy, King Saud University, PO Box 2457, Riyadh, 11451, Saudi Arabia
[d] Department of Clinical Medicine, College of medicine, AlMaarefa University, Dariyah, Riyadh, 13713, Saudi Arabia
[e] Respiratory Care Department, College of Applied Sciences, AlMaarefa University, Dariyah, 13713, Riyadh, Saudi Arabia
[f] Department of Emergency Medical Services, College of Applied Sciences, AlMaarefa University, Diriyah, 13713, Riyadh, Saudi Arabia
[g] Department of Nursing, College of Applied Sciences, AlMaarefa University, Dariyah, 13713, Riyadh, Saudi Arabia
[h] Department of Basic Medical Science, College of Medicine, AlMaarefa University, Dariyah, 13713, Riyadh, Saudi Arabia
[i] Department of Pharmacy Practice, College of Pharmacy, AlMaarefa University, Dariyah, 13713, Riyadh, Saudi Arabia

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ABSTRACT

Background & objectives: Pink salt and monosodium glutamate (MSG) are two typical food additives used in cooking to enhance flavour. However, excessive use of them has been associated to a variety of metabolic problems, including weight gain and hyperglycemia. The current study aimed to assess the metabolic changes caused by submaximal dosages of MSG and pink salt in experimental rats.

Methods: Twenty-four 120–150 g Wister rats of both sexes were divided into three groups: control, pink salt-treated (0.8 g/kg daily for three weeks), and MSG-treated (3.6 g/kg daily for three weeks). The body weight, amount of food and water consumed, and blood glucose levels of animals were measured and recorded as indicators of their metabolic changes. Furthermore, after salt treatments at intervals such as week 1, week 2, and week 3, the survival rate and general toxicity manifestations were determined. The results were statistically analysed using one-way ANOVA, with $p < 0.05$ being considered significant.

Results: The study found that the group given a submaximal dose of MSG gained significantly more weight ($p < 0.05$), consumed more food and water, and had higher blood glucose levels than the control. Ninety percent of the MSG therapy group survived by the end of the third week, however, they suffered from negative effects like abdominal distention, respiratory problems, ptosis, and subcutaneous swelling. On the other hand, the consumption of food and drink was significantly ($p < 0.05$) increased upon the administration of pink salt. Only little changes were observed in the body weight, blood sugar levels, and general features (such as subcutaneous

* Department of Pharmacy Practice, College of Pharmacy, AlMaarefa University, Dariyah, 13713, Riyadh, Saudi Arabia, sasdag@um.edu.sa/ sasdaq@gmail.com

E-mail addresses: syedrabbani09@yahoo.com (S.I. Rabbani), rorfali@ksu.edu.sa (R. Orfali), fahmad@mcst.edu.sa (F. Ahmad), grafi@mcst.edu.sa (R. Gilkaramenthi), mquadri@mcst.edu.sa (M.S. Ahmed Quadri), sasdaq@gmail.com, sasdag@um.edu.sa (S.M. Basheeruddin Asdaq).

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swelling, change in bowel colour, and loose stools). Additionally, it was shown that the survival rate remained unchanged, particularly after week 3.
Conclusion: According to study findings, MSG may induce metabolic issues, increasing the chance of death. While there was no discernible metabolic aberration linked to pink salt. Further research is required to fully understand the mechanism and consequences of these taste enhancers on the host system before pink salt can be deemed safe.

1. Introduction

Metabolic disease is currently one of the most common causes of morbidity and mortality in the population. Type-2 diabetes (adult-onset diabetes) is caused by the body's inability to properly use insulin. Over 95 % of patients with diabetes have type 2 diabetes. Type-2 diabetes is primarily caused by obesity and inactivity [1]. Although the defects begin early, complications appear later, leaving only a slim chance of restoring organ function [2]. Changes in blood glucose levels, food intake, and body weight are thought to be some of the first indicators of metabolic dysfunction [3].

Salts and other taste enhancers are essential in the preparation of foods. They are obtained from a variety of sources, including seawater, wells, lakes, and mines [4]. Sodium is a crucial component of these salts and is essential to the physiology of muscles and nerves. It has been suggested that eating too much salt can aggravate a number of conditions, including immune-mediated illnesses and hypertension [5].

The sodium salt of glutamic acid, a common amino acid used to improve food flavour, is called monosodium glutamate (MSG). In addition to being present in many foods and food additives, glutamic acid is also found in our bodies. The FDA views MSG as safe when taken in moderation. Nonetheless, there have been claims that it has negative health effects when consumed in large quantities, a condition known as "Chinese Restaurant Syndrome" [6]. MSG has also been linked to the development of chronic illnesses such as diabetes, dyslipidemia, and heart disease [7].

Obesity, brain damage, and other metabolic syndrome-related issues were observed in rodents injected with MSG in an experiment [8]. When MSG was given to test animals, it also raised the markers of dyslipidemia and fasting blood glucose [9]. Additionally, studies done on Chinese volunteers in good health showed that eating foods high in MSG increased the risk of gaining weight gradually [10]. Nevertheless, some research indicates that MSG is safe and does not play a significant part in the onset of metabolic disorders [11].

Rock salt, also known as pink salt, is made from minerals. Less sodium and significantly more calcium, iron, magnesium, potassium, aluminium, barium, silicon, etc. can be found in salt [12,13]. It is especially advised for patients with hypertension and mineral deficiencies to consume pink salt, as it has been shown to offer numerous health benefits [14]. However, extensive scientific evidence is required in the literature to support the beneficial effects of pink salt and its role in the metabolic process. In the current study, rats were used as experimental models to assess the metabolic effects of submaximal doses of pink salt and MSG. Additionally, the survival rate and effects of treatments on general characteristics were assessed.

2. Materials and methods

2.1. Animals

Twenty-four Wistar (12 males and 12 females) rats weighing 120–150 gm were used for the study. The animals were procured from procured from Central Animal House after approval (1703/0202/RC) from the Research Committee of the College of Pharmacy, AlMaarefa University, Riyadh. The rats were kept in a standard laboratory condition maintained at 25 ± 1 °C, 40–60 % humidity with photoperiod light/dark of 12/12 h and free access to water and pelleted food. The pellet food for rodents was procured from AlRabian Agro Food Company, Riyadh, Saudi Arabia. The total sodium content in the pellet diet was 0.50 g/kg. Animals were housed in plastic cages bedded with clean and dry husks. Animals were acclimatized for at least seven days before the beginning of the experiment. Humane care was taken to avoid any pain, distress, and discomfort to experimental animals during either transportation as well as while conducting the experimentation. The humane endpoint to terminate the study on the experimental rats was adopted before the start of the research. If any animal showed any one of the following signs such as dehydration, lethargy, respiratory distress, inability to reach food/water, lack of grooming, or appearance of tumor/ulceration, then the study was immediately terminated and the animals was shifted to rehabilitation, where medical care was provided to treat the animals [15].

2.2. Drugs and chemicals

Commercially available pink salt (HIMALAYAN, Al-Fares Food Processing Factory, Bahrain) and monosodium glutamate (MSG, AJI–NO–MOTO Foods Europe, Paris, France) were purchased from a local market. These salts are meant for human consumption and are of food-grade quality. All chemicals used in the study were of analytical grades meant research purposes.

2.3. Experimental design

The experimental rats were separated into three groups (n = 8), housing four animals (either male or female) in each cage.

Randomly selected rats were divided into the following.

Group-1: Control (1 ml/kg of sterilized normal saline, i.p for 3 weeks)

Group-2: Submaximal dose of pink salt (0.8 g/kg in distilled water sterilized by UV sterilizer (Novonic Ltd, Shanghai, China), daily for 3 weeks, i.p) [16,17],

Group-3: Submaximal dose of MSG (3.6 g/kg in distilled water sterilized by UV sterilizer, daily for 3 weeks, i.p) [6,18].

3. Preparation of salts and treatment protocol

The submaximal dose is the most tolerable, lower than the lethal dose, and is calculated as 1/5th of the LD_{50} value. The reported LD_{50} values for MSG and other salts are 18 g/kg and 4 g/kg in rats, respectively [6,16–18]. Hence, the submaximal dose of pink salt was calculated as 0.8 g/kg and MSG as 3.6 g/kg in the present study. Freshly prepared solutions of pink salt and MSG in distilled water were sterilized by UV sterilizer before administering to animals as per their body weight. The volume of the injection was adjusted to 1 ml/kg. Every alternate day, the weight of the animals was recorded, and the dose of the salts was recalculated accordingly. Continuous treatments were done for 3 weeks, taking almost care to avoid injecting the lumen of the intestine while administering the drug(s) and sterilizing the injection site before and after administering the test substance.

The parameters such as body weight, food intake, water intake, and blood glucose levels were employed to evaluate salts' metabolic effects on animals [19]. The values recorded on the first day of the study were considered baseline values (Table 1). Pelleted food and water sufficient for each group of animals were calculated, and after 24 h, the remaining quantity was measured to determine the food and water intake. The tail prick method under lidocaine-induced local anesthesia with the help of a sterilized needle was used to collect a small drop of blood and to measure blood glucose using a glucometer (CONTOUR, Bayers Ltd) [20]. The random blood glucose as well as the other parameters were recorded between 09:00 to 10:00 a.m. before administering the test substances. The values recorded for body weight, food intake, water intake, and blood glucose level on the first day of the study were considered as a baseline and were used to calculate the percentage change after week 1, week 2, and week 3, using the formula:

$$\text{Percentage change} = \text{Final value} - \text{Initial value}/\text{Initial value} \times 100$$

3.1. Survival rate

The survival rate was determined as per the method described in the earlier study [21] and it includes the number of animals alive from the total number at the end of the specific duration of the study.

3.2. General characteristics

The influence of a submaximal dose of pink salt and MSG on the general characteristics of the experimental animals was determined as per the previous research [22]. The observations recorded for each group of animals were categorized into 'eye,' 'skin,' 'excretion,' and 'others. The presence of a characteristic was recorded as a '+' sign (+ is mild, ++ is moderate, and +++ is severe), while the '– 'sign indicates the absence of the character. After the end of the study, the animals were kept for observation for ten more days to see any complications as well as to achieve a wash-out period, under the daily supervision of the researchers, and then returned to the central animal house facility.

3.3. Statistics

The results were expressed as mean ± SD and statistical analysis was done by One-way ANOVA using SPSS (Version 10.0) software followed by a post hoc test. One-way ANOVA was done separately conducted for each parameter. The data recorded for various treatments were compared and represented for different durations of exposure, followed by post-hoc analysis by Tukey's test. The results were represented in the form of figures and tables. The results' statistical significance was compared by comparing the treatment groups (pink salt and MSG) with the control. The values were considered significant statistically when $p < 0.05$.

4. Results

4.1. Baseline values of different parameters

Table 1 summarizes the baseline values of body weight, food intake, water intake and blood glucose levels. The data recorded on the first day of the experiment was considered as a baseline value and was subsequently used to calculate the percentage change at

Table 1
Baseline values of body weight, food intake, water intake, and blood glucose.

Body Weight (g)	Food intake (g/day/100 g body weight)	Water intake (ml/day/100 g body weight)	Random blood glucose (mg/dL)
134.8 ± 2.16	10.8 ± 0.46	8.4 ± 0.35	80.6 ± 1.35

Note: Values are represented as mean ± SD, n = 6.

different test durations.

4.2. Metabolic effects of pink salt and MSG at submaximal doses in experimental rats

The effect of a submaximal dose of pink salt and MSG on the percentage change in body weight is represented in Fig. 1. After one week of treatment, administration of MSG increased the percentage change in body weight significantly ($p < 0.05$) compared to the control animals. Similarly, MSG treatment in rats was found to increase the percentage change in body weight significantly after 2 weeks ($p < 0.01$) and 3 weeks ($p < 0.001$) compared to rats treated with normal saline. On the other hand, the submaximal dose of pink salt did not show significant variation in percentage body weight change compared to the control group at all the tested durations of treatment.

Effects of three weeks' administration of salts on the food intake indicated that pink salt at a submaximal dose enhanced the percentage intake of food significantly ($p < 0.05$) at a 3-week duration compared to the control group. However, pink salt at a 2-week duration did not significantly affect the percentage of food consumption. Further, the data suggested that MSG at submaximal dose enhanced the food intake at all three tested durations and was found to be significantly high at 1 week ($p < 0.05$), 2 weeks, and 3 weeks ($p < 0.001$) compared to the control animals (Fig. 2).

Percentage variation in the water intake after administration of submaximal doses of taste enhancers is indicated in Fig. 3. The observations suggested a negative change in water intake in the first week, while both pink salt and MSG treatments showed a positive significant ($p < 0.01$) increase in the percentage water intake compared to the control group. After 2-weeks, only MSG-treated rats were found to have increased their water intake significantly ($p < 0.001$) in comparison with the control. In addition, after 3 weeks the data indicated that pink salt treatment enhanced the percentage water intake significantly ($p < 0.05$), and MSG treatment showed more increase significantly ($p < 0.001$) compared to the control group.

The observations recorded for percentage change in blood glucose level suggest that pink salt at submaximal dose did not alter significantly at all three tested intervals. MSG at a submaximal dose did not affect any change in the percentage of blood glucose level after the first week of treatment. However, when the treatment of MSG was continued for 2 weeks a significant ($p < 0.01$) enhancement in percentage blood glucose level was observed compared to control animals and this change was further increased ($p < 0.001$) when the duration of MSG exposure was prolonged to three weeks (Fig. 4).

4.3. Effect of pink salt and MSG at submaximal doses on survival rate in rats

The data collected to determine the survival rate after administering the submaximal dose of pink salt suggested that the treatment did not induce any change. Similarly, the survival rate in control animals after treating them with normal saline for 3-weeks did not produce any mortality. However, the survival rate with a submaximal dose of MSG after 3 weeks of treatment was found to be 90 %, although the administration for 1-week and 2-weeks did not induce deaths in the experimental animals (Fig. 5).

4.4. Effect of pink salt and MSG at submaximal dose on the general characteristics in rats

The general characteristics recorded in animals after administering a submaximal dose of pink salt and MSG is represented in Table 2. The observations suggested that the treatment of salts for one week did not induce any change in general characteristics. However, after 2 weeks, MSG-treated rats showed breathing difficulty and abdomen distension. After 3-weeks, pink salt-treated animals showed subcutaneous swelling, change in bowel color, loose stools, and soiling of the perineum. MSG treatment was found to show ptosis, subcutaneous swellings, loose stools, breathing difficulties, gait alteration, and abdominal distension after 3 weeks of treatment.

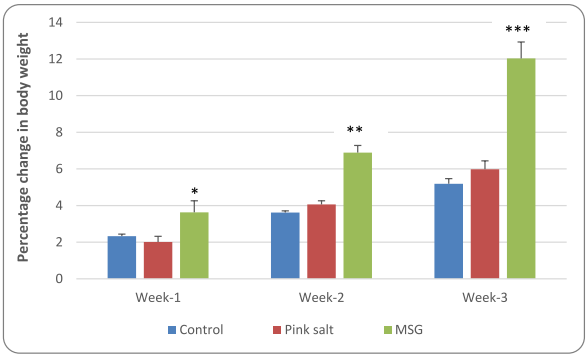

Fig. 1. Effect of salts on percentage change in body weights.

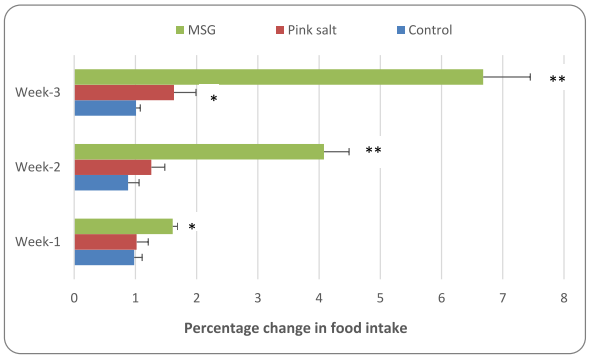

Fig. 2. Effect of salts on percentage change in food intake.

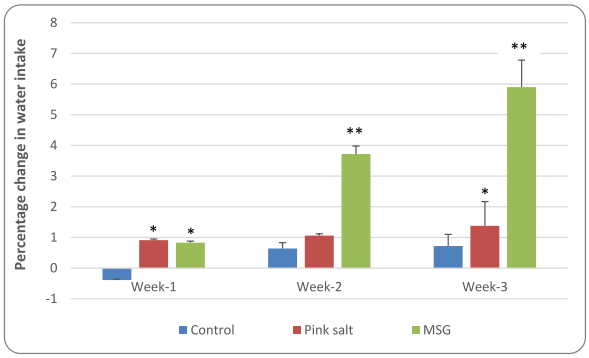

Fig. 3. Effect of salts on the percentage change in water intake.

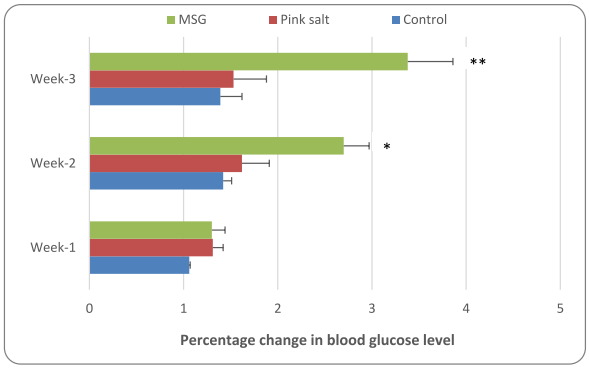

Fig. 4. Effect of salts on the percentage change in blood glucose levels.

5. Discussion

In this study, the effects of pink salt and monosodium glutamate (MSG) on general and metabolic characteristics were assessed, and the survival rate was determined (Figs. 1–4 and Tables 1 and 2). After giving the taste enhancers to the experimental rats continuously for weeks one, two, and three at submaximal dosages, the data was recorded. During the three test durations, the percentage of body weight was not significantly impacted by the administration of pink salt. When compared to the control group, MSG was found to significantly increase the percentage change in body weight at weeks 1 ($p < 0.05$), 2 ($p < 0.01$), and 3 ($p < 0.001$) (Fig. 1). The results corroborate previous studies in which rats given MSG continuously experienced a progressive increase in body weight [10].

Prior research has suggested a potential connection between MSG and obesity in both animal and human studies [12]. The results of the studies indicated that MSG had a favourable effect on the brain's hunger centres [23]. The current study clearly shows how MSG improves food intake. When compared to the control animals, the observations revealed that the MSG treatment increased the percentage of food intake significantly ($p < 0.05$) from the first week of treatment onward, and by week 2, the variation was highly

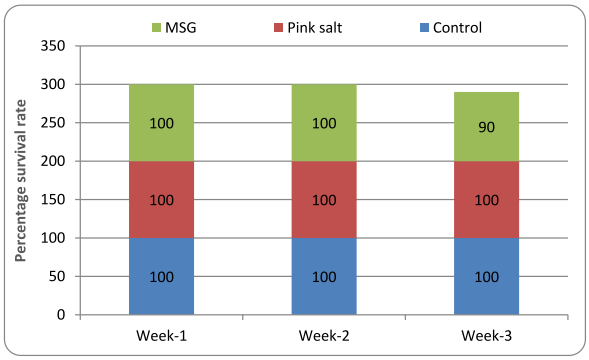

Fig. 5. Effect of salts on survival rate.

Table-2
Effect of salts on the general characteristics.

Parameters		Week-1			Week-2			Week-3		
		Gp-1	Gp-2	Gp-3	Gp-1	Gp-2	Gp-3	Gp-1	Gp-2	Gp-3
EYE	Eye dullness	–	–	–	–	–	–	–	–	–
	Eye opacity	–	–	–	–	–	–	–	–	–
	Pupil dilatation	–	–	–	–	–	–	–	–	–
	Ptosis	–	–	–	–	–	–	–	–	+
SKIN	Change in hair color	–	–	–	–	–	–	–	–	–
	Skin texture abnormality	–	–	–	–	–	–	–	–	–
	Subcutaneous swellings	–	–	–	–	–	–	–	+	+
EXCRETION	Change in bowel color	–	–	–	–	–	–	–	+	–
	Loose stools	–	–	–	–	+	–	–	+	++
	Wetness or soiling of perineum	–	–	–	–	–	–	–	+	–
OTHERS	Abnormalities in teeth	–	–	–	–	–	–	–	–	–
	Breathing difficulties	–	–	–	–	–	+	–	–	++
	Gait alteration	–	–	–	–	–	–	–	–	+
	Abdomen distention	–	–	–	–	–	+	–	–	++

Note: Gp-1 = Control, Gp-2 = Pink salt treated, Gp-3 = MSG treated.
Absence (–), Mild presence (+), Moderately presence (++) of the characteristic.

significant ($p < 0.001$) (Fig. 2). It has been discovered that long-term MSG use is linked to body weight gain due to fat deposition and elevated plasma leptin levels [11,12].

The results shown in Fig. 3 indicate that giving pink salt to animals for three weeks increased their percentage of water intake significantly ($p < 0.05$) when compared to the control group. Research from the past has shown that consuming an excessive amount of salt ($Na+$) for an extended period of time increases the intake of water, most likely as a way to help the body excrete ions [24]. The administration of MSG was found to be more effective in stimulating this effect, as evidenced by the significant increase in the significance level from $p < 0.05$ in the first week to $p < 0.001$ in the second and third weeks when compared to the control group (Fig. 3). Previous research has shown that taking MSG continuously results in the body retaining salts, which increases the amount of water that is consumed [25]. Increasing water intake was also proposed as a contributing factor to weight gain in people who regularly eat food containing MSG [23].

Following three weeks of pink salt treatment, the percentage change in blood glucose level showed no discernible change at the submaximal dose in comparison to the control. However, in contrast to the control group, MSG caused a significant ($p < 0.01$) percentage increase in blood glucose levels after the second and third weeks of continuous treatment (Figure-4). The results are consistent with previous studies that found that administering MSG to humans caused hyperglycemia [9]. According to the studies, the administration of MSG may result in glucose intolerance via several mechanisms, including insulin resistance and a malfunctioning beta cell secretory mechanism. For MSG-induced metabolic defects, it has also been proposed that the involvement of mammalian targets of rapamycin (mTOR) proteins results in glucagon dysfunction [9,26].

The survival rate of the experimental animals following submaximal exposures to MSG and pink salt is another intriguing finding of the study. According to the observations, pink salt administration did not cause mortality in rats; however, rats treated with MSG for three weeks experienced 10 % of deaths (Fig. 5). The results support previous research that suggested chronic MSG administration is linked to death in experimental settings [27].

Extended exposure to monosodium glutamate (MSG) has been linked to multiple adverse effects, including impaired renal, hepatic, cardiovascular, brain, and endocrine system functioning. Following the MSG administration, significant fibrotic and inflammatory changes were also seen in key organs like the liver, kidney, and heart [28]. The overall features of this investigation showed that MSG

therapy resulted in dyspnea, distension of the abdomen, diarrhoea, and additional side effects (Table 2). Although pink salt administration caused subcutaneous swelling, a change in stool colour, loose stools, and wetness, the presence of more severe complications, as well as defective metabolism, may have contributed to a 10 % mortality rate with MSG. Previous studies on MSG found toxic manifestations in vital organs such as the liver, kidneys, brain, and thymus [29], which could be one of the causes of death observed in our study.

The current investigation assessed a few of the significant precursors of metabolic alterations and general traits brought on by the submaximal dosage of MSG and pink salt. A shorter duration of exposure to the salt solution, a low statistical power to discern differences between sexes, a small number of metabolic variables, and a restricted measurement of pain and distress markers on the experimental animals throughout the study period are some of the study's limitations. As a result, additional research is required to determine the complete metabolic effects and safety of pink salt and MSG using various experimental models.

6. Conclusion

The results of this investigation showed that administering the submaximal dose of monosodium glutamate (MSG) raised blood glucose levels, food and water intake, and body weight percentage. Moreover, MSG altered the general characteristics and had a negative impact on the survival rate. Although these changes were found to be minor, they require further investigation. However, administration of pink salt increased food and water intake and changed certain general characteristics without exhibiting many complications. Therefore, more research is needed, with a focus on determining the mechanism and establishing the comprehensive role of these food enhancers in various organ system functions.

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Ethics declarations

This study was reviewed and approved by Research Committee of the College of Pharmacy, AlMaarefa University, Riyadh, Saudi Arabia (1703/0202/RC).

Data availability

Data included in article/supp.material/referenced in the article.

CRediT authorship contribution statement

Thamer Abdullah Alharbi: Conceptualization. **Syed Imam Rabbani:** Writing – review & editing. **Raha Orfali:** Conceptualization. **Moneer E. Almadani:** Investigation. **Fuzail Ahmad:** Investigation. **Rafiulla Gilkaramenthi:** Project administration. **Ebtesam Abdulrahman Jibreel:** Methodology. **Mohammed Sharique Ahmed Quadri:** Writing – original draft, Resources. **Syed Mohammed Basheeruddin Asdaq:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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