# A LANDSCAPE OF MONOSODIUM GLUTAMATE ON HOMOSAPIENS

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## ABSTRACT:

Monosodium glutamate (MSG), a commonly used flavour enhancer, in almost all savory foods. However, there are still unanswered health-related problems surrounding MSG use in humans. Research suggests that MSG is the root cause of a number of diseases, including obesity, the Chinese syndrome disorder, redox imbalance, and adverse effects on reproduction. Similarly, additional clinical research contradicts MSG's unfavorable health effects and demonstrates its positive effects on issues like appetite, salt intake, and bone development, etc. This article reviews the research on the beneficial and harmful effects of MSG on homo sapiens. MSG was regarded as safe by the WHO, US FDA, United Nations Food and Agriculture Organization, and many other regulatory bodies, although it shouldn't be consumed in amounts that exceed.

## INTRODUCTION

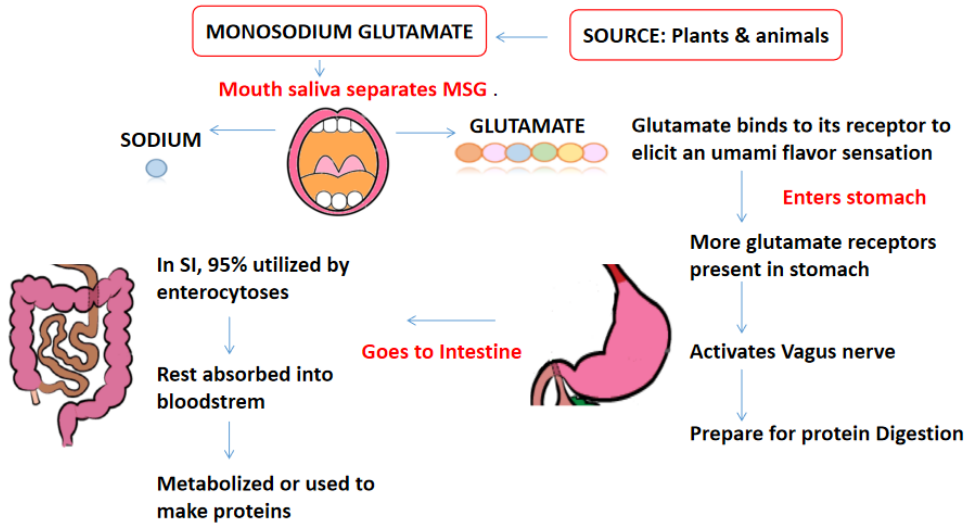
The consequences of using the flavor enhancer monosodium glutamate (MSG) on human health are essential to be discussed. (1)Worldwide, the food industry frequently uses monosodium glutamate (MSG) to enhance the flavor of food. (2)Although food safety regulators usually consider this as safe but some studies have expressed concern about its long-term safety. MSG treatment has been linked in preclinical investigations to premalignant changes, cardiotoxicity, hepatotoxicity, and neurotoxicity. MSG use has been linked to genotoxic effects in lymphocytes, increased oxidative stress and apoptosis in thymocytes, and cancer. (3)Commercial foods are now the lifeline of the urban population by saving time and resources, but their nutritious content is sacrificed. One of the most often used food additives is monosodium glutamate. According to several research, MSG is hazardous to developing fetuses, children, adolescents, and adults. Hypertension, obesity, digestive tract issues, and impairment of brain, neurological system, reproductive, and endocrine system function are physiological complications occurred by MSG toxicity. MSG's impact is influenced by its dosage and manner of delivery. (11) MSG imparts to processed meals a distinct aroma known as umami in Japanese and is also termed China salt in many nations and it is one of the variants of glutamic acid, has been used to season food for more than a century and also referred to as "Chinese Restaurant Syndrome. Humans can normally metabolize significant amounts of glutamate, which is synthesized in the gut through the process of protein degradation by exopeptidase enzymes. For mice and rats, the median fatal dose (LD50) ranges from 15 to 18 g/kg body weight. It is categorized by the European Union as a food additive that is allowed in specific foods but has a quantitative limit. (13) In Europe, the daily

intake of glutamate from food is ranged between 5 and 12 g. and it is considered safe to consume up to 16,000 mg/kg of body weight. Even in a large dose, GLU won't enter fetal circulation. When there is a decline in appetite, monosodium-L-glutamate can be used in low doses to increase palatability. (15)

**Chinese restaurant syndrome**

The Chinese restaurant syndrome evolved from an anecdotal life of discomfort after eating Chinese food. The causative agent has been identified as monosodium glutamate.(50)

A set of symptoms following the consumption of a Chinese supper was originally recorded in 1968 and referred to as Chinese Restaurant Syndrome.(28) This syndrome is caused by monosodium L-glutamate, which can induce headaches. It generates burning sensations, face pressure, chest discomfort in adequate dosages and Individuals' oral threshold ability varies significantly.(49) the researchers conducted a multi-center DBPC challenge research with 130 patients to examine the reaction of subjects who report symptoms from MSG consumption. Large dosages of MSG administered without meals may evoke greater symptoms than a placebo in people who feel they respond negatively to MSG. When MSG was administered with meals, no reactions were detected.(28) Double-blind testing of those who claim to have the syndrome' has failed to confirm the involvement of monosodium glutamate as the stimulating agent.(50) The validity of the symptoms experienced by many people after consuming monosodium glutamate (MSG) has largely remained unanswered, owing to a scarcity of well-designed challenge experiments. The total and average severity of symptoms were larger after MSG administration than after placebo ingestion. Rechallenge demonstrated a 2.5 gm MSG apparent threshold dosage for a response was found by applying the Oral Challenge with MSG-replicated symptoms to claimed sensitive individuals.(27) Monosodium L-glutamate could relate to vitamin B6 deficiency by the neurological reactions known as the Chinese Restaurant Syndrome. Double blind experiments revealed that the signs of this Syndrome to oral glutamate do not reoccur after treatment, and vitamin B6 biochemistry is important in the cause of the Chinese Restaurant Syndrome.(45)




**EFFECT ON KIDNEY**

Increasing evidence reveals the role of the glutamate receptors, cysteine-glutamate antiporter, and -ketoglutarate dehydrogenase in the up-regulation of MSG-induced kidney oxidative damage.(61) to ascertain the impact of extended MSG consumption on the mass of mesangial cells in the kidneys, this study result shows that indirect constriction of the glomerular capillary lumen, which results in kidney failure, was the cause of the observed mesangial

mass expansion, indicated by hypertrophy and hyperplasia.(62) Serum creatinine, potassium, sodium, and citrate levels as well as urine output volume were considerably greater in MSG-treated rats. But ammonium and magnesium urinary excretion were also lesser. MSG Intake causes alkaline urine which may increases the kidney stones risks with hydronephrosis in rats.(63) Rats' GFR and CRPF increased with the addition of MSG to their diets, and their absolute salt reabsorption increased as well. In rats given MSG, hyperfiltration coexisted with a typical response to glycine infusion. Na retention in the body was decreased by the NMDAR antagonist MK-801, but the percentage of reduction was noticeably larger in the group that consumed more MSG.(64) Significant alterations in the gross morphology of the kidneys were seen in albino mice exposed to MSG during the neonatal period. Consistent findings in experimental animals included enlarged urinary volume and proximal convoluted tubules (PCT) and distal convoluted tubule (DCT) dilatation. Both PCT and DCT lining cells had decreased height and lost their luminal microvilli.(65) In this study, the cytotoxicity of aspartame was histologically assessed using hematoxylin and eosin (H and E) stains. Small necrotic patches with light vacuolation, an expanded and clogged central vein, and an accumulation of fat droplets have all been documented. Glomeruli in renal tissues appeared with cavity constriction, congestion, bleeding, disintegration, and swelling. (66) This review investigates biomarkers of MSG using murine models. Adult male Wistar rats were given three different types of control water, including sodium chloride and sodium bicarbonate, or water with 1 g% MSG. The findings showed MSG has characteristics that are comparable to those of NaHCO3, an alkalinizing agent, in terms of producing a particular urinary metabolic pattern, causing alkaline urine, and limiting the absorption of bicarbonate by the kidneys. These findings, in our opinion, will be helpful in the investigation of the effects of MSG on humans.(1) Consumption of high-fat, high-fructose (HFF) meals or monosodium glutamate (MSG) alters the gut flora and promotes the emergence of a number of disorders. Hamsters fed MSG+HFF displayed kidney damage. These findings suggest that consuming MSG and HFF together increases the risk of kidney damage, causes gut dysbiosis, and raises p-cresol sulphate levels in hamsters.(6) The kidney cortex of adult albino Wistar rats was examined in the current study together with the effects of a control group by administered MSG intraperitoneally. histomorphometry of kidney tissue demonstrated a substantial difference in the length of the glomeruli and the size of the bowman's capsule with elevated bowman's space. Researchers have discovered that MSG is hazardous to many body organs when used as a food additive, hence its use as such may need to be discontinued.(9) There is significant evidence that MSG consumption causes kidney injury through oxidative stress, although the underlying processes remain unknown and this review highlights some information from research on MSG-induced kidney oxidative damage, potential causes, and their significance from a toxicological viewpoint. (17)

**EFFECT ON REDOX STATUS**

MSG, a dietary ingredient in pre-packaged foods, has been demonstrated to be harmful to both humans and experimental animals. Banerjee A et al investigated the undesired changes by taking MSG more than recommended and to assess the effects, three different MSG dosages were studied in rats , and found that MSG induced an inflammatory response, an increase in body weight, dyslipidemia, and hepato-cardiac marker enzyme. The MSG high dose group demonstrated a significant effect, indicating that MSG should not be used in food preparation and also changes in redox status suggest oxidative stress. (4) At days 2, 4, 6, 8, and 10 of life, Wistar rats were injected with monosodium L-glutamate at a dosage of 4 g/kg body weight. Glutathione levels in the kidney dropped, whereas glutathione peroxidase (GPx) activity increased. ROS may be involved in the inactivation of NO as well as the reduction of renal plasma flow and glomerular filtration rate. Changes in liver redox state cause a

reduction in SOD and an increase in GPx activity and are responsible for the functional and histological changes in kidney and liver.(55) The liver, kidney, and brain of rats were subjected to MSG-induced oxidative damage for the purpose of this investigation into the modulatory effects of dietary antioxidants vitamin C, vitamin E, and quercetin. Additionally, in a rat bone marrow micronuclei model, the impact of these antioxidants on the potential genotoxicity of MSG was examined. VIT E was ineffective at preventing the genotoxicity that MSG causes. The results demonstrate that dietary antioxidants have protective potential against oxidative stress generated by MSG and, in addition, suggest that active oxygen species may play an important role in its geno toxicity.(5)The study looked at how MSG supplementation affected the redox state and neurochemical indicators in nymphal lobster cockroaches. Increased ROS, NO, Fe2+, Fe2+, and MAO activity were also generated by MSG supplementation, although there was no dose-dependently significant difference in the amount of dopamine present. The neurotoxic effects seen with sub-chronic intake of high quantities of MSG may have a biochemical explanation including increased oxidative and cholinergic activities and lower dopamine levels.(67) Upon giving MSG subcutaneously to adult male mice, the erythrocyte glucose level was significantly increased with more lipid peroxidation.The body counteracted the oxidative stress caused by MSG by sustaining the glutathione level, which was accomplished by increasing metabolizing enzyme activity.(68) Singh, K. et al. explored MSG's impact on oxidative stress in adult mice by evaluating ROS biomarkers in cardiac tissue and the finding suggests that increased oxidative stress could be an additional factor for atherosclerosis progression.(69)

**EFFECT ON REPRODUCTION**

MSG develops reproductive anomalies in males and causes various reproductive dysfunctions including spermatogenic alteration resulting in a low sperm count, high sperm abnormality, reduced live sperm, and decreased sperm pH along with gonadotropin imbalance, blood hemorrhage, distorted germ, and Sertoli cells. (71)This study aimed to assess how MSG, at average human daily intake (ADI) affected the sperm quality and alterations in the reproductive organs of adult male rats. Sperm quality significantly decreased when MSG was present at an estimated ADI of 120 mg/kg body weight as compared to the control and MSG60 groups. Additionally, analysis of the oxidative status revealed that MSG therapy causes oxidative stress in the testes, more so at a dose of 120 mg/kg body weight. This study demonstrates that an MSG ingestion amount of 120 mg/kg body weight may seriously harm the reproductive system. (8) MSG negatively affects male rat reproduction by lowering plasma levels of testosterone and luteinizing hormone, sperm count & weight of the testicles (LH). Curcumin and propolis coadministration, either independently or together, reduces these effects and restores testicles' weight and the structure of seminiferous tubules with sperm-filled lumen (72) The observation of this study on animals revealed that MSG raises NF-B levels in the blood, testicular fluid, and epididymis tissue fluid. The degradation of spermatogenesis, edema in a lumen in testicular tissues, and detachment and vacuolation of the seminal epithelium were all observed histological alternation in the reproductive organs.(74)This investigation looked at the effect of MSG on LH and testosterone levels in adult male rat serum. According to the findings, blood testosterone levels M2 considerably varied from the control group (p 0.01) while serum LH levels significantly reduced after 45 days of MSG therapy. This study reveals that MSG has an impact on male reproductive systems both directly and indirectly.(75) This present research focused to investigate in vivo toxic effects of MSG on the uterus of adult female rats as well as in vitro study utilising cells. The progesterone and estrogen level were significantly changed in the MSG-treated animals and exhibited strong affinity binding to acetylcholine receptors and interfered with normal nerve transmission. this plays a role in oxidative stress in the female

reproductive system .Therefore, when using this substance, care should be given, especially for females who are at risk for hormonal imbalance. (2) Cellular hypertrophy, as well as degenerative and atrophic alterations, were significantly altered in the investigation of MSG's effect on the ovaries of Sprague Dawley rats. These results demonstrate that MSG caused significant structural alterations, including the degeneration of follicles, oocytes, and the medulla, which had vacuoles with clogged blood arteries. (73)

**EFFECT ON OBESITY**

Ka He et al examined the relationship over time between MSG consumption and the prevalence of overweight .In this study, 10,095 seemingly healthy Chinese people between the ages of 18 and 65 were evaluated for a longitudinal relationship between MSG usage and the prevalence of overweight. To calculate the change in BMI, multilevel mixed-effects models were built, and the prevalence of overweight was calculated using Cox regression models with gamma-shared frailty. After adjusting for age, physical activity, total calorie intake, and other significant lifestyle variables, the adjusted hazard ratio of overweight was 1.33 for individuals in the highest percentile of MSG intake compared to those in the lowest quintile.(10) Another study demonstrates relationship between (MSG) consumption and overweight in humans by investigating 752 healthy Chinese (48.7% of them were women). The daily consumption was 0.33 grams on average (SD = 0.40) and the Prevalence of overweight was significantly higher in MSG users .This study presents evidence based on human subjects that consuming MSG may raise the risk of obesity, irrespective of physical activity or total calorie intake.(76) the pathophysiological pathways and metabolic changes connected to obesity and observed result shows that MSG-induced obesity-related inflammation and decreased adiponectin were more prominent in male mice, while glucose tolerance, insulin sensitivity, and redox balance were altered with increased age and suggests that the metabolic alterations are associated with gender as well as aging.(77) Garlic, ginger, and turmeric can help to reduce these side effects. MSG's influence on human health can also be mitigated by eating foods high in vitamins C and E, as well as other antioxidants. Locust bean has been claimed to be an excellent substitute for MSG-containing condiments. (58)

**EFFECT ON STOMACH**

Glutamate (Glu) can influence stomach physiological activities such as secretion and motility. The apical membrane of main cells in the lower area of fundic glands and the somatostatin-secreting D-cell fraction of the stomach mucosa were found to have Glu receptors. The addition of monosodium Glu (MSG) to an amino acid-rich meal lacking Glu increased acid, pepsinogen, and fluid production.(19) MSG is known to have an effect on the endocrine system and gastrointestinal (GI) motility; investigated MSG affect on glucose homeostasis, incretin secretion, and stomach emptying following a lipid-containing meal in people by using single-blind placebo-controlled cross-over research. A 400 mL liquid meal containing MSG or NaCl was served and found that MSG had no effect on either the half-gastric emptying time or the postprandial symptoms. This effect was presumably attributable to stimulation of glucagon-like peptide-1 secretion rather than a change in stomach emptying.(21) Researchers investigated the effects of L-Glutamate enrichment of a protein-rich liquid meal on stomach emptying, as well as analogous enrichment of an equal carbohydrate meal or noncaloric water. According to the findings, A carbohydrate supper had no substantial influence on gastric excretion and free glutamate is required for protein digestion and useful in treating delayed stomach emptying.(23) according to our most recent investigations on young pigs fed greater (4-fold) than usual dietary amounts of glutamate. The majority of glutamate molecules are either oxidised or converted by the mucosa into other non-essential amino acids .Since glutamate is a crucial excitatory amino acid, the

gastric mucosa's developing neuronal receptors, which are underdeveloped in preterm newborns, may serve to aid in gastric emptying.(80) This research examined the effects of MSG on gastric emptying and duodenal motility in 10 healthy male volunteers. After consuming a liquid meal with and without 0.5% MSG, coronal pictures were taken. After 60 minutes, stomach residual volume steadily reduced in all individuals, and four of eight subjects responded favorably to MSG. These results suggest that MSG accelerates gastric and duodenum emptying in subjects with positive responses to MSG.(81)

**EFEECT ON APPETITE**

This influence on food selection reflects by changing the flavor and aroma of various food, particularly by employing MSG, which is an effective strategy to influence food choices without producing hyperphagia.(38) Consumption of monosodium glutamate (MSG) is suggested to activate physiological and metabolic effects, Following a crossover design, thirteen healthy people were given a nutritional dosage of MSG (2 g) or sodium chloride as a control for 6 days.MSG supplementation had no effect on subjective assessments of hunger or fullness. (24) The researchers investigated the impact of adding MSG to carrot soup either with or without whey protein on subjective hunger, food consumption (FI), and satiated hormones in healthy young men. MSG enhanced fullness and lowered the urge to eat, and when combined with protein, it lowered blood glucose while increasing insulin and C-peptide.(34) This research investigated 16 males and 42 females to find out the effect of habitual exposure to umami stimuli on umami taste perception, hedonics, and satiety. A month-long diet strong in umami stimuli reduces perceived umami flavor and hunger for savoury items. After MSG treatment, the desire to consumption of savoury foods is reduced. (37) When combined with protein, MSG has been found to improve satiety. Inosine 5'-monophosphate abundant in high-protein sources, acts synergistically with MSG when tasted, and it may promote satiety. MSG/IMP added to a low-energy preload exhibited a biphasic impact on appetite, promoting appetite during consumption and increasing post-ingestive satiety. (41) The addition of MSG to foodstuffs improves its umami flavor, acceptability, and intake. Other highly palatable compounds, such as sugar and fats, improve appreciation for novel tastes with which they are regularly associated, particularly when consumed. When glutamate is combined with a novel flavour, it can condition liking for that flavour. While glutamate's post-ingestion effects may be pleasant, flavor conditioning cannot be excluded out.(44) Descriptive and electronic-tongue studies were performed on 10 MSG alternatives, which were mixtures of three commercial items, as well as MSG. When taken alone or in mixes, the MSG replacements exhibit varied sensory properties, implying the presence of synergistic or inhibitory effects among them. When replacing MSG, consider the features of each proposed substitution in respect to the specific food system.(48)

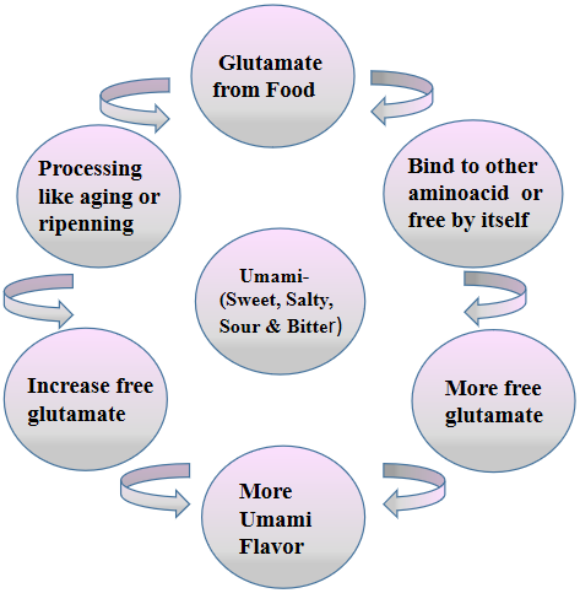



**Fig.2. Monosodium glutamate as a taste enhancer**

**EFFECT ON BONE**

Appropriate protein intake is essential for healthy bone growth and subsequent attainment of a greater peak bone mass. The effects of varied doses of MSG supplementation on bone properties in Balb/C mice were studied. Glutamate can serve as a functional amino acid for bone physiology and can support individual with poor bone status by glutamate supplementation. MSG use preserved bone quality by increasing collagen production, but it did not allow for normal bone development. Cortical bone was shown to be less responsive to protein limitation than trabecular bone in a study of bone microarchitecture.(25)In this study, bone marrow chromosomal aberration and bone marrow micronucleus assays on mice were used to examine the genotoxic effects of MSG. The albino mice were divided into standard (cyclophosphamide 100 mg/kg), test (MSG), and control. All results, with the exception of those obtained at a dosage of 250 mg/kg, were statistically significant (P 0.01) when compared to the control. Monosodium glutamate decreased the mitotic index (MI) and induced micronuclei in normochromatic erythrocytes in a dose-dependent manner, suggesting its potential to be clastogenic. (82) Mice's bone and bone marrow histogenesis are examined in relation to the impact of MSG. In the bone marrow of the MSG-treated mice, there is a large accumulation of adipose tissue together with receding hemopoietic tissue. These pathological alterations are a result of the drug's effects on the hydrolysis of the enzyme alkaline phosphatase, glycolysis involved in bone deposition, or hormones secreted that cause bone resorption.(84) Cross linker is needed in tissue engineering, particularly in bone scaffolds, to improve the connectivity between the pores. In this analysis, MSG was used to develop four distinct scaffolds with varying crosslinker concentrations. The scaffold with 10% MSG concentration as a crosslinking agent had the greatest mechanical qualities and the lowest water adhesion test results.(85)

**EFFECT ON ASTHMA**

Even in patients with a history of MSG-induced asthma, the existence of the condition has not been shown conclusively. Allen et al. (1987) tested 32 asthmatic volunteers with oral monosodium glutamate (MSG) challenges and found that 14 of them reacted to MSG.Four further studies have been done, and none of them have validated the findings of the summary.(16) Medications, such as aspirin and sulfites, are increasingly being identified as

causes of sudden severe asthma. this study investigated the asthma-inducing potential of monosodium L-glutamate on 32 asthmatic patients and found that MSG causes a dose-dependent response that can last up to 12 hours, making identification harder for both the patient and the clinician.(26) MSG challenges failed to cause asthma symptoms in participants with and without a reported sensitivity to MSG. Subjects with a history of MSG sensitivity exhibited no significant percent drop in values following placebo challenges compared to MSG 2.5 g oral challenge. The investigation is necessary to retain a healthy skepticism about the presence of MSG sensitivity in asthmatics.(32) This study designed an MSG challenge procedure that is randomized, double-blind, placebo-controlled, and statistically reliable for detecting early and late asthmatic symptoms in a person with asthma. Twelve participants with clinically confirmed asthma and a belief that MSG caused their asthma, were enlisted. No immediate or definite late asthma responses were found, according to the findings.(87)

**EFFECT ON PAIN**

The International Classification of Headache Disorders, third edition, lists MSG as a chemical that causes headaches (ICHD-III beta). only limited The research has not been thoroughly studied to determine the cause of the association between MSG and headaches. (14)The analysis was a double-blind, placebo-controlled, crossover trial to examine at the incidence of side effects such as headache and discomfort after taking MSG. After MSG administration, there was a substantial increase in headache reporting and subjectively perceived pericranial muscle discomfort. When compared to the low MSG and placebo sessions, the high MSG session had higher systolic blood pressure.(36) MSG is thought to be connected with headaches and craniofacial problems such as temporomandibular disorders. This study examined about how the administration of MSG affects muscular pain sensitivity prior to and after experimentally induced muscle pain in 16 healthy persons. The primary outcome of this investigation was that systemic MSG consumption has no effect on pain intensity or pressure pain sensitivity in the masseter and temporalis muscles that were injected with glutamate.(35)A randomised, double-blind, placebo-controlled research was carried out to explore the effect of high-dose MSG ingestion on glutamate concentration in the masseter muscles as determined by microdialysis and muscular pain sensitivity. Every day, 32 healthy individuals drank 150 mg/kg monosodium glutamate (MSG) or NaCl diluted with a 400 mL soda. Pressure pain threshold, tolerance to pressure pain, autonomic indicators and reported adverse effects were also evaluated. Excessive repeated MSG consumption has no effect on interstitial glutamate levels in the masseter muscle in healthy men.(30)

**EFFECT ON ELDERLY PATIENTS**

For three months, 0.5% monosodium L-glutamate (MSG) added to rice gruel three times a day improved the behavioral and nutritional condition of hospitalized elderly.The study was conducted with Fourteen subjects in the MSG group and 15 in the control group.Only the MSG group showed a significant improvement in mealtime behaviour. the ratio of reduced-form albumin to total albumin raised exclusively in this group. (29) In dementia patients, continued consumption of monosodium L-glutamate (MSG) has an influence on cognitive performance and dietary score. This was a single-blind, placebo-controlled study with 159 dementia patients in a hospital. At the follow-up evaluation, the TDAS total scores in the MSG group improved significantly more than those in the Control group. Our findings imply that long-term MSG consumption has an influence on cognitive function. Patients with higher scores on the palatability measure demonstrated greater improvement in cognitive function.(33) A sensory loss that affects taste and smell perception is seen in the majority

of aged people. Age-related loss of taste and smell might result in poor food intake and a compromised nutritional status. Monosodium glutamate (MSG) can be added to meals to improve the sensory experience, boost immunity and salivary flow, and decrease oral complaints.(88) During a 2-month period, 11 elderly inpatients had meals fortified with MSG and its effects on their nutritional status, overall health, and quality of life (QOL) were examined. Even in the absence of changes in protein consumption or nutritional condition, the degree of recognition was enhanced, and peripheral lymphocytes increased. The findings imply that Glutamate should be used appropriately for senior nutritional care in order to enhance QOL.(89) This paper investigates the potential use of MSG supplementation in improving nutrition in patients with poor nutrition and the elderly. It indicates that this impact is mediated by certain receptors found on taste buds as well as in other areas of the GIT.(90)

**EFFECT ON SALTINESS**

An Acceptable Daily Intake (ADI) of 30 mg/kg body weight/day was established in 2017 by a European Food Safety Authority decision on the use of glutamate and related salts as food additives. An EFSA statement issued in 2021 proposed unifying the creation of Health-Based Guidance Values for nutrients that are also controlled chemicals (including food additives). Glutamate plays an important function in nitrogen balance. In the splanchnic region, glutamate is heavily metabolized.(52) This mechanism is saturable because glutamate emerges dosage-dependently in the circulation following a large dose of glutamate loading and the body tries everything it can to minimise glutamate bioavailability, which may be neurotoxic in excess. If glutamate is never taken alone, its bioavailability will be restricted, if not insignificant, and no detrimental consequences are to be predicted in adult people.(53)The purpose of this study is to evaluate MSG's effect on the saltiness or palatability of low-salt solutions. According to the research, umami can alleviate the loss of palatability caused by salt reduction, and adding an acceptable amount of an umami ingredient can allow salt reduction from 0.9 to 0.3% without reducing palatability.(47) MSG is recognized as a Generally Recognized as Safe (GRAS) substance by the US FDA and the Federation of American Societies for Experimental Biology. MSG is used to lower salt levels in some processed foodstuffs, and considered the safety of MSG as a food additive(56)This research examined the effect of MSG on the saltiness and palatability of low-salt solutions. The 0.3%, 0.6%, and 0.9% NaCl solutions were tasted by Japanese subjects either with or without the 0.3% MSG. Palatability was rated as being better with MSG than without MSG, whereas MSG increased saltiness. In order to ease salt reduction in the diet while retaining palatability, an adequate amount of umami components can be added. (91)

In this study, the effect of MSG was examined in relation to the sensory attributes of the NaCl/MSG complex and the actual food system. When meat products were supplemented with binding agents, MSG had a potential use in the formulation of meat products as a partial NaCl replacement or a salt enhancer.(92) this study examined the MSG effect on the sensory qualities and hedonic perception of sodium or sugar-reduced samples. According to the observations, salty and umami flavor intensity enhanced while sourness and bitterness decreased in the samples.(93)

**EFFECT ON CNS**

In the central nervous system, glutamate is the primary excitatory neurotransmitter. and also serves important physiological function like sensory role. MSG absorption in the diet does not cause in considerable increases in glutamate concentrations in the blood, unless when administered experimentally in doses much beyond usual intake levels.(57)

MSG in

gestion should be kept to a minimal minimum due to its tendency to cause oxidative stress and neurological toxicological effects at high doses. Increased oxidative, cholinergic, and monoaminergic activity, along with a reduction in dopamine levels, might provide a reasonable molecular explanation for the neurotoxic effects found with sub-chronic MSG use.(67) In this study, rats fed a meal containing 70 g/kg of MSG had their oxidation state, cholinesterase levels, and brain histology measured. The findings showed that MSG consumption raised plasma malonedialdehyde levels, reduced RBC superoxide dismutase, glutathione peroxidase, and plasma catalase activity, and increased brain and plasma true cholinesterase concentrations.(94) Studies have shown that high doses of MSG produce neurotoxic or excitotoxic effects on neurons in the central nervous system. In Sprague-Dawleyrats, the greatest MSG concentration raised the percentage of damaged neurons in three Cornuammonisareas of the hippocampus in MSG-supplemented mice. This increased the degree of dose-dependent hippocampus cell death. (95) Animal studies have demonstrated its toxicity, but most of them used different delivery techniques and levels than those used in human MSG use. Monosodium glutamate results in an increased glutamate level, which causes excitatory toxicity and can have serious negative effects on the central nervous system, including severe neurological impairment.(96)

**EFFECT ON METABOLISM:**

Hugues Chevassus et al examined the impact of glutamate on insulin secretion and glucose tolerance in humans using 18 healthy volunteers. The results indicate that oral (L)-glutamate stimulates glucose-induced insulin secretion in a concentration-dependent way.(39)

Glutamate is associated with the glycolytic process, especially when combined with glucose.This study examines the effects of carbohydrate consumption on circulatory glutamate levels. In both the glutamate and carbohydrate trials, plasma glutamate concentrations were significantly higher than at baseline and Moreover, MSG and carbohydrate supplementation can be employed to alter plasma glutamate when dosing is staggered.(42) The current study aimed to investigate the effect of MSG on intestinal amino acid metabolism. The study indicated that the portal hyperglutamatemia observed quickly after ingestion of an MSG-supplemented meal is most likely due to saturation of the intestinal ability to metabolise glutamate, with no demonstrable modification of the metabolic activities regulating glutamate metabolism in enterocytes.(54)

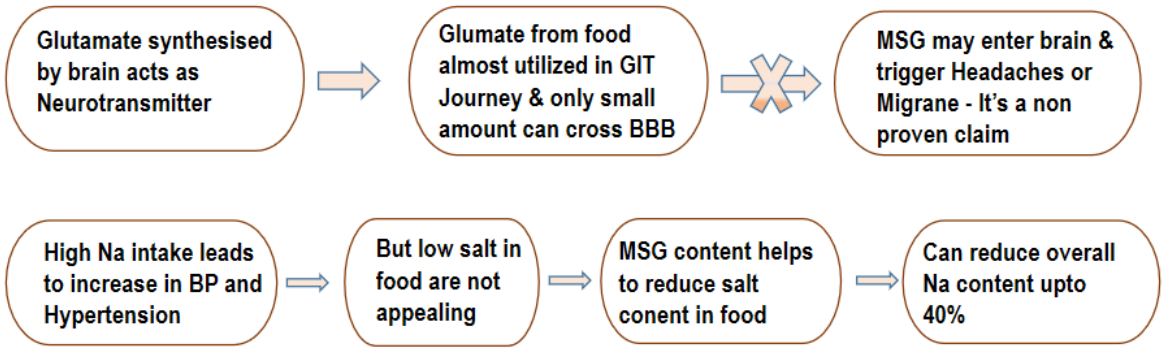



Fig.3. Assessment Highlights

Table.1.

| EFFECTS | CLINICAL & NON CLINICAL STUDY FINDINGS | ANIMALS/ HUMAN SUBJECS | REF |
|---|---|---|---|
| **Kidney** | 1. Indirect constriction of the glomerular capillary lumen, which results in kidney failure, was the cause | Adult male rats 15 mg/kg | 62 |

| | | | |
|---|---|---|---|
| | of the observed mesangial mass expansion, indicated by hypertrophy and hyperplasia | | |
| | 2.Serum creatinine, potassium, sodium, and citrate levels as well as urine output volume were considerably greater | Adult male Wistar rats (2 mg/g body weight MSG/day) | 63 |
| | 3.Rats' GFR and CRPF increased and Na retention in the body was decreased by the NMDAR antagonist MK-801 | Male Wistar rats (5 weeks old) (3 g/kg b.w./day) | 64 |
| | 4.Both proximal convoluted tubules (PCT) and distal convoluted tubule lining cells had decreased height and lost their luminal microvilli. | Albino mice 2mg/gram | 65 |
| | 5.Glomeruli in renal tissues appeared with cavity constriction, congestion, bleeding, disintegration, and swelling. | Mice at doses of 360 mg kgG1 /day for one month, | 66 |
| | 6.consuming MSG and high-fat, high-fructose meals together increases the risk of kidney damage, causes gut dysbiosis, and raises p-cresol sulphate levels in hamsters | Hamsters 20 mg/ml of MSG into drinking water | 6 |
| | 7.substantial difference in the length of the glomeruli and the size of the bowman's capsule with elevated bowman's space. | Adult albino Wistar rats (4 mg MSG/g body weight) | 9 |
| **Redox Status** | 1. MSG induced an inflammatory response, an increase in body weight, dyslipidemia, and hepato-cardiac marker enzyme and also changes in redox status suggest oxidative stress. | Adult male albino Wistar rats (200, 400, &600 mg/kg) for 28 days | 4 |
| | 2. Changes in liver redox state cause a reduction in SOD and an increase in GPx activity and are responsible for the functional and histological changes in kidney and liver. | Neonate male Wistar rats (4 g/kg body weight) | 55 |
| | 3. The neurotoxic effects seen with sub-chronic intake of high quantities of MSG may have a biochemical explanation including increased oxidative and cholinergic activities and lower dopamine levels | nymphs of lobster cockroaches (0.1 mg/g, 1 mg/g, 10 mg/g, and 100 mg/g) | 67 |
| | 4. the erythrocyte glucose level was significantly increased with more lipid peroxidation. | Normal adult male mice. (0,4 & 8 mg/g of body weight) | 68 |
| | 5. increased oxidative stress could be an additional factor for atherosclerosis progression | Normal adult male mice (0, 4 and 8 mg/g body weight) | 69 |
| **Reproduction** | 1. MSG induces oxidative stress in the testis andcould cause significant damage to the reproductive system. | adult male rats (60 ,120 mg/kg) | 8 |
| | 2.Lowering plasma levels of testosterone and luteinizing hormone, sperm count & weight of the testicles (LH) | adult male albino rats (4 g/kg body weight) | 72 |
| | 3.The degradation of spermatogenesis, edema in a lumen in testicular tissues, and detachment and vacuolation of the seminal epithelium | Adult male Wistar rats (60 ,120 mg/kg) | 74 |
| | 4. MSG treatment was significantly reduces serum LH level and have a direct & indirect effect on male reproductive organs. | Mature male rats (4mg.g BW) | 75 |
| | 5. progesterone and estrogen level were significantly changed in the MSG-treated animals and exhibited | Adult female Sprague Dawley rats (2 g/kg) | 2 |

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| | strong affinity binding to acetylcholine receptors and interfered with normal nerve transmission. | | |
| | 6.MSG caused significant structural alterations, including the degeneration of follicles, oocytes, and the medulla, which had vacuoles with clogged blood arteries | female Sprague-dawley rats (0.10, 0.15,and 0.20g/kg) | 73 |
| **Obesity** | 1. MSG consumption was positively, longitudinally associated with overweight development | 10,095 healthy adults- China Health & Nutrition Survey (CHNS) | 10 |
| | 2. Consuming MSG may raise the risk of obesity, irrespective of physical activity or total calorie intake. | 752 healthy Chinese<br>- cross sectional study | 76 |
| **Stomach** | 1. stimulation of glucagon-like peptide-1 secretion rather than a change in stomach emptying. | 13 healthy male volunteers-Randomised, single-blind,cross-over study (2 g, 0.5% wt:vol) | 21 |
| | 2. free glutamate is required for protein digestion and useful in treating delayed stomach emptying. | Ten healthy men, Randamoised double blind study (0.5% wt:vol) | 23 |
| | 3. MSG accelerates gastric and duodenum emptying in subjects with positive responses to MSG. | Ten healthy male volunteers 0.5% MSG | 81 |
| **Appetite** | 1. Employing MSG is an effective strategy to influence food choices without producing hyperphagia. | Sixty two hospitalized diabetics participants, Randamoised study; 0·6% MSG | 38 |
| | 2. MSG enhanced fullness and lowered the urge to eat, and when combined with protein, it lowered blood glucose while increasing insulin and C-peptide | Fifty-two healthy young men, Randomized repeated-measures Design (5 g, 1% w/w) | 34 |
| | 3. A month-long diet strong in umami stimuli reduces perceived umami flavor and hunger for savoury items. | Fifty-eight healthy participants, A parallel-group, single-blind, randomized controlled study design, 3.8 g MSG | 37 |
| | 3. .MSG added to a low-energy preload exhibited a biphasic impact on appetite, promoting appetite during consumption and increasing post-ingestive satiety | Twenty-seven volunteers within-participant design, 0.6% wt:wt MSG | 41 |
| | 4. The addition of MSG to foodstuffs improves its umami flavor, acceptability, and intake | 69 subjects<br>0.5% MSG | 44 |
| **Bone** | 1. MSG use preserved bone quality by increasing collagen production, but it did not allow for normal bone development. | 12 eight-week-old Balb/C female mice (2%, 1%, 0.5%, 0.1%, and 0.05% MSG) | 25 |
| | 2. Monosodium glutamate decreased the mitotic index (MI) and induced micronuclei in normochromatic erythrocytes in a dose-dependent manner, suggesting its potential to be clastogenic | Swiss albino mice of Mus musculus species (250, 455, 500 and 1000 mg/kg MSG) | 82 |
| | 3. In the bone marrow of the MSG-treated mice, there is a large accumulation of adipose tissue together with receding hemopoietic tissue. | 20 young adult female mice, (2, 4, and 6 mg/g MSG) | 84 |
| **Asthma** | 1. MSG causes a dose-dependent response that can last up to 12 hours, making identification | 32 asthmatic patients, single-blind, placebo- | 26 |

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| | harder for both the patient and the clinician | controlled study, 0.5 gm to 5.0 gm MSG | |
| | 2. MSG challenges failed to cause asthma symptoms in participants with and without a reported sensitivity to MSG. | 100 subjects with asthma,single-blind, placebo-controlled screening challenges, 2.5 g of MSG | 32 |
| | 3. No immediate or definite late asthma responses were found, according to the findings. | Twelve subjects with asthma and a perception of MSG induced asthma,1 & 5 gm MSG | 87 |
| **Pain** | 1. When compared to the low MSG and placebo sessions, the high MSG session had higher systolic blood pressure. | 14 healthy men, double-blinded, placebo-controlled, crossover study,MSG (75 or 150 mg/kg) | 36 |
| | 2. MSG consumption has no effect on pain intensity or pressure pain sensitivity in the masseter and temporalis muscles that were injected with glutamate | 16 healthy adult subjects, randomized, double-blinded, placebo-controlled study, MSG (150 mg/kg) | 35 |
| | 3. Excessive repeated MSG consumption has no effect on interstitial glutamate levels in the masseter muscle in healthy men | 32 healthy individuals, randomized, double-blinded, placebo-controlled study,(150 mg/kg MSG) | 30 |
| **Elderly patients** | 1. MSG group showed a significant improvement in mealtime behaviour | 19 participants ,double-blind placebo controlled trial, 0.5% (w/w) MSG | 29 |
| | 2. Long-term MSG consumption has an influence on cognitive function. Patients with higher scores on the palatability measure demonstrated greater improvement in cognitive function | 159 subjects with dementia, single-blind, placebo-controlled trial, MSG (0.9 g/dose) | 33 |
| | 3. Even in the absence of changes in protein consumption or nutritional condition, the degree of recognition was enhanced, and peripheral lymphocytes increased. | 11 elderly inpatients, 0.5% w/w MSG | 89 |
| **Saltiness** | 1. Umami can alleviate the loss of palatability caused by salt reduction, and adding an acceptable amount of an umami ingredient can allow salt reduction from 0.9 to 0.3% without reducing palatability | 584 healthy participants, multicenter study, 0.3% MSG. | 47 |
| | 2. In order to ease salt reduction in the diet while retaining palatability, an adequate amount of umami components can be added. | 561 participants, 0.3% MSG | 91 |
| | 3. Salty and umami flavor intensity enhanced while sourness and bitterness decreased in the samples | 600 consumers, MSG concentrations of 0.01%, 0.04%, and 0.16% (w/v) | |

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| **CNS** | MSG consumption raised plasma malondialdehyde levels, reduced RBC superoxide dismutase, glutathione peroxidase, and plasma catalase activity, and increased brain and plasma true cholinesterase concentrations | 54 Sprague Dawley male albino rats, 70 g MSG/ kg diet | 94 |
| | 1. The greatest MSG concentration raised the percentage of damaged neurons in three Cornuammonisareas of the hippocampus in MSG-supplemented mice | 25 white male Sprague-Dawleyrats, 2, 4and 6 mg/ gram MSG | 95 |
| **Metabolism** | 1. glutamate stimulates glucose-induced insulin secretion in a concentration-dependent way | 18 healthy volunteers, double-blind placebo-controlled cross-over study, 10 g MSG | 39 |
| | 2. MSG and carbohydrate supplementation can be employed to alter plasma glutamate when dosing is staggered. | 9 participants (MSG; 150 mg/kg body weight) | 42 |
| | 3. Portal hyperglutamatemia observed quickly after ingestion of an MSG-supplemented meal is most likely due to saturation of the intestinal ability to metabolize glutamate | 8 weaned male Large White pigs, 10 g monosodium glutamate | 54 |

**IN FAVOR CLINICAL FINGDINGS**

Glutamate is a major component of dietary protein taken in the form of monosodium glutamate (MSG).Glutamate is both a vital neurotransmitter and an important precursor for bioactive compounds such as glutathione. The essential role of glutamate as an oxidative fuel may have therapeutic promise for improving newborn gut function. When at higher dietary intakes, the rate of MSG absorption is greater when administered intragastrically rather than intraduodenally (22). Over a 5 day period, 71 healthy volunteers were given placebos and MSG dosages of 1.5, 3.0, and 3.15 g/person, representing a body mass adjusted dose range of 0.015-0.07 g/kg body weight before a standardised meal.

The majority of subjects (86%) and MSG (85%) did not respond to the therapies.

Previously attributed to MSG sensations did not occur at a significantly higher incidence than those produced by placebo therapy. There was a significant (P 0.05) negative connection bet ween MSG dose and after effects. The current investigation concluded that

'Chinese Restaurant Syndrome' is an anecdote used to treat a range of postprandial ailments; thorough and actual scientific proof tying the syndrome to MSG was not identified. (20)

The JECFA has assigned monosodium glutamate (MSG) an "ADI not defined," indicating that there are no toxicological risks related to its usage as a food additive. The question is whether excursions over a numerical ADI are possible, which would undermine the premise of no danger. Even among those who claim idiosyncratic resistance to such foods, the use of MSG in ethnic cuisines does not reflect a situation in which intakes may reach dangerous levels. Neonatal studies have demonstrated that the human newborn can metabolize glutamate as effectively as adults, and babies are no more at risk of harmful consequences from MSG consumption than adults.(31) The incidence of responses to monosodium glutamate (MSG), in people with chronic urticaria was evaluated with 65 people. With 95% certainty, the study concluded that MSG is a rare exacerbate of chronic idiopathic urticaria. (40)

The frequency of responses observed following monosodium glutamate (MSG) ingestion is debatable. This multicenter, multiphase, double-blind, placebo-controlled crossover trial was conducted to examine MSG-related responses. The findings imply that large doses of MSG administered without meals may evoke greater symptoms than a placebo in people who believe they react adversely to MSG. However, no long-term or significant consequences of MSG intake have been detected, and the results were inconsistent when tested again. (43)
Fifty-seven participants with fibromyalgia (FM) and irritable bowel syndrome (IBS) were given a 4-week diet free of food excitotoxins such as MSG and aspartame. Participants with improved on the dieting were randomly assigned to a two week double-blind placebo-controlled crossover trial with MSG or placebo for three days consecutively per week. These data imply that dietary glutamate may be contributing to the fibromyalgia symptoms in certain cases.(46).

**CONCLUSION:**

The most often used flavor enhancer, monosodium glutamate, still has several unresolved health-related issues in people. Research indicates that MSG is the primary factor in a number of disorders, including obesity, the Chinese syndrome condition, redox imbalance, and harmful effects on reproduction. Similar to this, other clinical research refutes MSG's adverse health effects and shows its beneficial effects for issues like appetite, salt consumption, bone growth, etc. MSG's positive and negative effects of MSG on homo-sapiens are described in this article. MSG has been considered safe by the WHO, US FDA, UN Food and Agriculture Organization, and many other regulatory authorities, although it shouldn't be consumed in levels that exceed.

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