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Toxicity of monosodium glutamate intake on different tissues induced oxidative stress: A Review

Aljohara M. Al-Otaibi[1], Nahed M. Emam[2], *Hala Kamel Elabd[2] and*

Nadeen Ibrahim Esmail[2]

[1]Department of Biology, College of Science, Princess Nourah bint Abdulrahman University, 13225, Saudi Arabia
[2]Zoology Department, Faculty of Science, Arish University, Egypt

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Abstract:

Monosodium glutamate (MSG) is one of the commonest food additives in the developed world and it is commonly used as a flavor enhancer. MSG can be found in various concentrations in numerous food products. It is the salt of glutamic acid, one of the naturally occurring amino acids. **Aim of work:** the present review was prepared to illustrate the effects of Monosodium Glutamate on different vital tissues like pulmonary tissues, brain, liver, kidney, testes, and others. Monosodium glutamate treatment showed numerous pathological changes in different vital tissues like the lung, including highly congested blood vessels, granuloma, ruptured bronchial walls, narrowed alveolar sacs, fibrosis, and increased collagen fibers which might induce oxidative stress Also, Monosodium glutamate treated rats showed decreased DNA content and increased protein content, increased amyloid–β protein content and increased PAS +ve materials in different tissues. **Conclusion**: the present study concluded that monosodium glutamate consumption led to numerous dystrophic changes in different tissues which might induce oxidative stress Therefore, MSG is considered a toxic agent due to increased production of ROS, so that, the ingestion of this substance by humans should be reviewed and great attention must be directed towards this substance to avoid its highly desirable uses.

Keywords: Monosodium glutamate, tissues, lung, brain, nervous system

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Introduction

Monosodium Glutamate (MSG) is one of the most widely used food additives all over the world and is a part of many commercial foods as a flavor enhancer at home, in restaurants, and by food processors. Studies providing evidence of MSG's toxic effects have raised the increasing interest in MSG intake as a flavor enhancer.[1, 2]

Monosodium glutamate (MSG) is the sodium salt of glutamic acid (GA), one of the most abundant naturally occurring nonessential amino acids. It is sold as a fine white crystalline substance, similar in appearance to table salt (NaCl) and sugar **as shown in the next figure (A)**

Figure A: showing monosodium glutamate powder.

Glutamic acid (GA) is present naturally in most foods, such as meat, poultry, seafood, and vegetables. [3] Glutamate is present in nature in two main forms, free form and the form bound to peptides and proteins. It is added either as the purified monosodium salt or as a component of a mix of amino acids and small peptides resulting from the acid or enzymatic hydrolysis of proteins. [4]

Bera *et al.* [5] stated that the use of MSG as a food additive and the natural level of glutamic acid in foods are not toxicological concerns in humans. Agriculture Organization and World Health Organization placed it in the safest category for food additives. United States food and drug administration (FDA) concluded that MSG is safe when 'eaten at customary levels' and, although a subgroup of otherwise healthy individuals develops an MSG symptom complex when exposed to 3 g of MSG in the absence of food, MSG as a cause has not been established because the symptom reports are anecdotal. A popular belief is that large doses of MSG can cause headaches and other feelings of discomfort, known as **'Chinese Restaurant Syndrome** (CRS), but double-blind tests fail to find evidence of such a reaction. International and national bodies governing food additives currently consider MSG safe for human consumption as a flavor enhancer. The European Union classifies it as a food additive permitted in certain foods and subject to quantitative limits.

The body uses glutamate as a neurotransmitter in the brain and there is glutamate-responsive tissue damage in other parts of the body. Moreover, it has been reported that MSG has neurotoxic effects resulting in brain cell damage, retinal degeneration, an endocrine disorder, and some pathological conditions such as addiction, stroke, epilepsy, brain trauma, neuropathic pain, schizophrenia, anxiety, depression, Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis. [6]

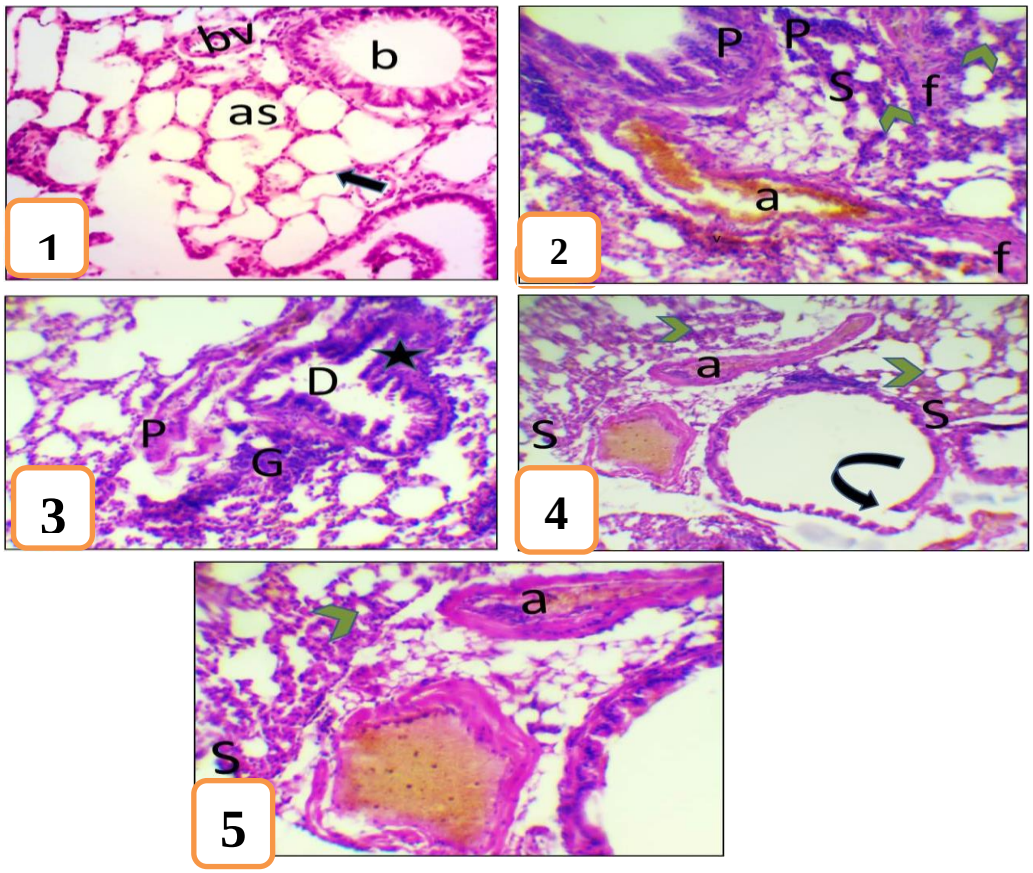
The human body also produces glutamate, and it plays an essential role in normal body functioning. However, many studies highlighted the adverse effects of MSG when consumed**.** Glutamate at high doses produces numerous severe histopathological changes [7], neuronal degeneration [8], and oxidative damage in different organs. [9] MSG exposure caused several maternal and fetal changes; therefore, it is considered an embryotoxic agent, and mothers must avoid the administration of this substance during the gestation period. MSG showed swollen cytoplasm, dark pyknotic nuclei, and loss of neurons in the placenta. [10] Also, **Shredah**[7] concluded that MSG is a genotoxic agent to gingival tissue that has deleterious effects on DNA and

the molecular findings were supported in a dose-dependent manner. Administration of MSG-induced hypothalamic neurotoxicity accompanied by metabolic disorders, including obesity, transient insulin resistance, and metabolic alterations in the blood lipotoxicity in the liver and skeletal muscle. MSG inhibited leptin signaling and plays a critical role in the regulation of body weight. In another possibility, noncontrolled leptin reaction may lead to insulin resistance which is a fundamental aspect linked to a wide array of diseases including hypertension, hyperlipidemia, and atherosclerosis [(11)].

It has been reported that the injection of glutamate into laboratory animals intraperitoneally at a dose of 4 mg/g body weight has resulted in a marked increase in malondialdehyde (a lipid peroxidation marker) formation in the liver, the kidney, and brain of rats and decrease glutathione level (the body master antioxidant) triggered by MSG in the three organs [(9)]. Recent studies in infant pigs showed that consumption of glutamate at higher (four-fold) than normal dietary quantities resulted in oxidation or metabolization of its molecules by the mucosa into other nonessential amino acids [(12)]. Conventional toxicity studies carried out on MSG administered with diet in several species did not reveal any specific toxic or carcinogenic effects nor were there any adverse effects in reproduction and teratology studies [(13)]. Also, MSG can cross the blood-brain barrier to reacting with brain receptors causes' brain destruction. Moreover, it was shown that high levels of glutamate might be related directly or indirectly to cancer and obesity [(5)]. Neurotoxic effects on the brain, obesity, metabolic defects, and detrimental effects on sex organs are the most discussed in the connection with MSG intake, especially the effect of MSG on the liver, kidney, testis, and epididymis which might cause increased oxidative stress in the tissues of animals. [(2)]

MSG symptoms complex include headache, muscle tightness, numbness tingling, general weakness, and flushing. severity. severity and frequency of symptoms both were greater as compared with placebo some of the reaction after eating MSG includes abdominal discomfort, urticarial, ventricular arrhythmia, asthma, neuropathy (dysfunction of peripheral nerves particularly numbness and weakness), and topic dermatitis (inflammation of the skin resulting in itchy, red, swollen, and cracked skin [(12)]. Preclinical studies have associated (MSG) with cardiotoxicity, hepatotoxicity, neurotoxicity, low grad _inflammation, metabolic disarray, and premalignant alteration, along with behavioral changes. moreover, links between MSG consumption and tumorigenesis increased oxidative stress and apoptosis in thymocytes, as well as the genotoxic effect in lymphocytes have been reported. [(13)]

According to **Al-Otabi** [(14),] lung tissues of pregnant mice from MSG-treated animals showed extensive tissue damage, alveolar hemorrhage, severely damaged bronchioles, and cellular infiltration in the lung tissues as shown in the next figure (figs. 2-5)



Figs. (B): showing highly affected lung tissue of the T group with numerous pathological changes. According to Al-otabi[14], These changes include: highly elongated, congested, and corrugated arterial walls (a), presence of granuloma (G), highly thickened ( ) or ruptured ( ) bronchial walls, narrowed alveolar sacs (➢), highly thickened alveolar septa (S), fibrosis(f) with numerous pyknotic nuclei (P) in walls of the bronchioles and arterial walls which contain hemolyzed blood cells **(figs. 2-5**).

Abu Elnaga *et al*. [15] showed that short-term MSG exposure caused several maternal and fetal changes. Therefore, MSG is considered an embryotoxic agent, and mothers must avoid the administration of this substance during the gestation period.

Mosaad and Sabry [16] reported that daily oral administration of a high dose (8g/kg b.wt. MSG) for a long duration (3 months) on young male and female Albino rats significantly increased serum tumor necrosis factor –α (TNF-α) and interleukin-1β (IL1-β) levels in the treated groups.

MSG killed body cells and caused neuroendocrine disorders in the experimental animals, and it caused an adverse reaction in humans. Free glutamic acid is combined with sodium, and it is a neurotransmitter that caused nerves to die. MSG acted as excitotoxin [17].

Effect of MSG on Cerebrum:

Our brain consists of excitatory principal neurons and inhibitory interneurons which interact in an effective way creating a functional balance to avoid any disease. So, changes in neuronal excitability can cause neural network modifications and possible pathological consequences. Additionally, Glutamate receptor hyperactivation could lead to neuronal death in several brain regions, such as the cerebral cortex, cerebellum, and hippocampus [18]. Oxidative stress has been described as an important feature of neuronal injury and is characteristic of many neurodegenerative diseases. Because of high levels of oxygen consumption by the central nervous system, it is susceptible to free radical damage. MSG consumption has been reported to be related to alterations in the antioxidant status in different brain areas, the superoxide dismutase and catalase activity are strong indications of oxidative stress in the brain that decreased with increasing doses of MSG. This leads to decreasing cells with progressive loss of neurons, cellular inflammation, and cellular swelling. Also, an increase in microglia cell density (astrocytes) suggests a response of toxicity, as astrocytes play an important role in glutamate homeostasis and the reuptake of free glutamate, thus, preventing glutamate excitotoxicity [19]

Effect of MSG on Cerebellum MSG:

One of its main components is glutamate. So, it may have caused the death of Purkinje cells due to excessive activation of glutamate receptors. It leads to motor function disruption and functional impairment. The most common signs of cerebellar diseases involve ataxia, impaired body balance, anxiety disorders, vertigo, and dizziness. Ocular instability and nystagmus may occur as the cerebellum plays a major role in eye movement control (control of calibration and maintenance of ocular alignment) [20].

Monosodium Glutamate And Cancer:

According to the American Institute for Cancer Research, studies to uncover MSG's potential ill effects began in the late 1960s. At that time, some people began to believe that the additive in dishes they ate at Chinese restaurants made them sick. Since that time, scientists have looked and have not found a link between monosodium glutamate and cancer [21].

Monosodium glutamate causes obesity:

MSG may influence you to overeat, leading to obesity. Researchers from the University of North Carolina did a study among people in rural China to examine the effects of MSG. They chose that region because most people there prepare their meals at home without processed foods but still use a lot of MSG. Those who used the most MSG were also the most likely to be overweight, regardless of how their total calories and levels of physical activity compared with those who used the least. In other studies, mice are injected with MSG for the very purpose of causing them to become obese. Scientists think MSG causes lesions in the brain and interferes with its processing of leptin[22,23]. Leptin is a hormone that signals to the brain that you have had enough to eat, and it shuts off your appetite and increases your calorie burning. Problems with leptin signaling, called leptin resistance, are factors in obesity.

Monosodium glutamate poisoning:

Other terms for MSG are Chinese restaurant syndrome, glutamate-induced asthma, hot dog headache, and MSG syndrome. The term **(Chinese restaurant syndrome)** was first used in the 1960s to describe the symptoms experienced by some people after eating in Chinese restaurants. Monosodium glutamate poisoning refers to a cluster of symptoms recognized as an adverse reaction to MSG. The symptoms include headache, sweating, flushing, heart palpitations, weakness, chest pain, and nausea. [24] Other symptoms are tightness in the face and burning, numbness, and tingling in the face and neck.

MSG on pregnant and lactating women: It is common practice for expectant women to eat a varied and well-balanced diet and consume enough calories to ensure a healthy pregnancy. To facilitate fetal growth and

development, most amino acids are actively transported across the placenta. Research indicates that amino acid concentrations are higher in the fetus, regardless of what the mother consumes ([25].

Both the placenta and fetal liver play important roles in amino acid (and specifically glutamate) transport and metabolism important for fetal development [26]

In rodent studies, researchers investigated the effects of dietary intake of MSG on reproduction and birth. The study looked at three generations of mice that were fed a daily intake of up to 7.2 g/kg of MSG. No adverse effect was observed in each generation, nor was there evidence of any incident of brain lesions in the neonates. Besides research on the fetus, scientists also investigated the effect of MSG ingestion on lactation and breastfed infants. Upon examination of lactating women who consumed MSG at 100 mg/kg of body weight, researchers noticed no increase in the level of glutamate in human milk and no effect on the infant's intake of glutamate. American Academy of Pediatrics Committee stated that MSG has no effect on lactation and poses no risk to the consuming infant [27,28]

According to **Anca *et al*** [29], numerous negative effects were reported by preclinical studies (Figure **C**). The route of administration is another important issue that must be addressed, with effects varying accordingly, as presented in Figures **D**, **E**, and **F**. Subcutaneous or intraperitoneal administration of high doses in preclinical studies has little, if any, relevance to dietary human exposure, as they bypass the normal metabolic pathway of orally ingested MSG.

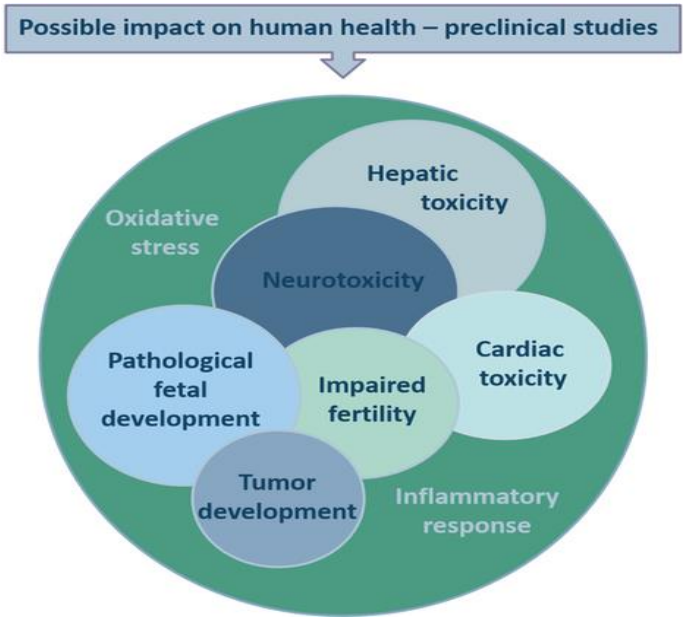


Figure C: Possible impact on human health—extrapolation from preclinical studies.

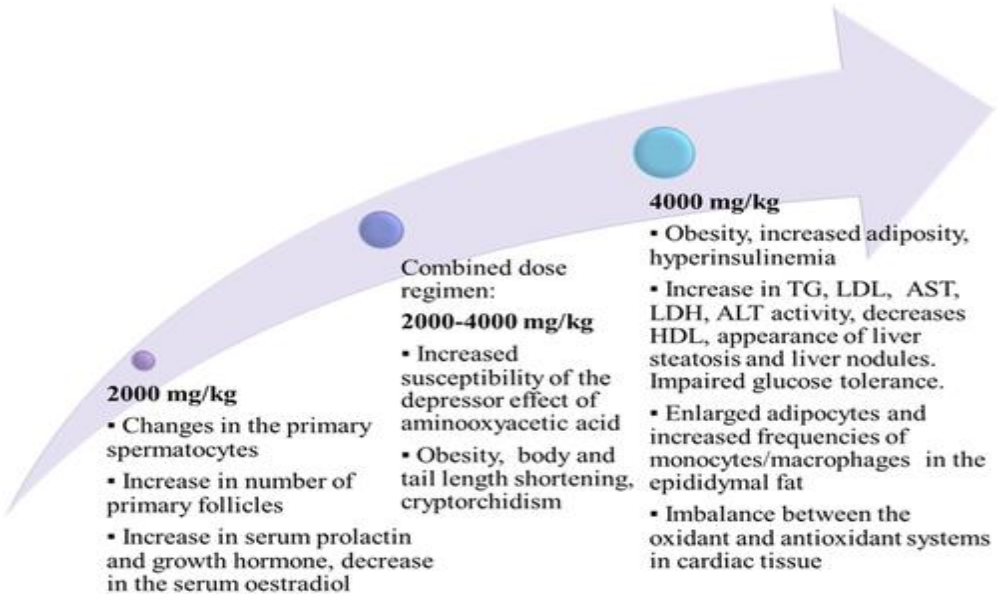


Figure D: Acute exposure in newborn rodents—parenteral administration.
TG, triglycerides; LDL, low-density lipoproteins; HDL, high-density lipoproteins; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

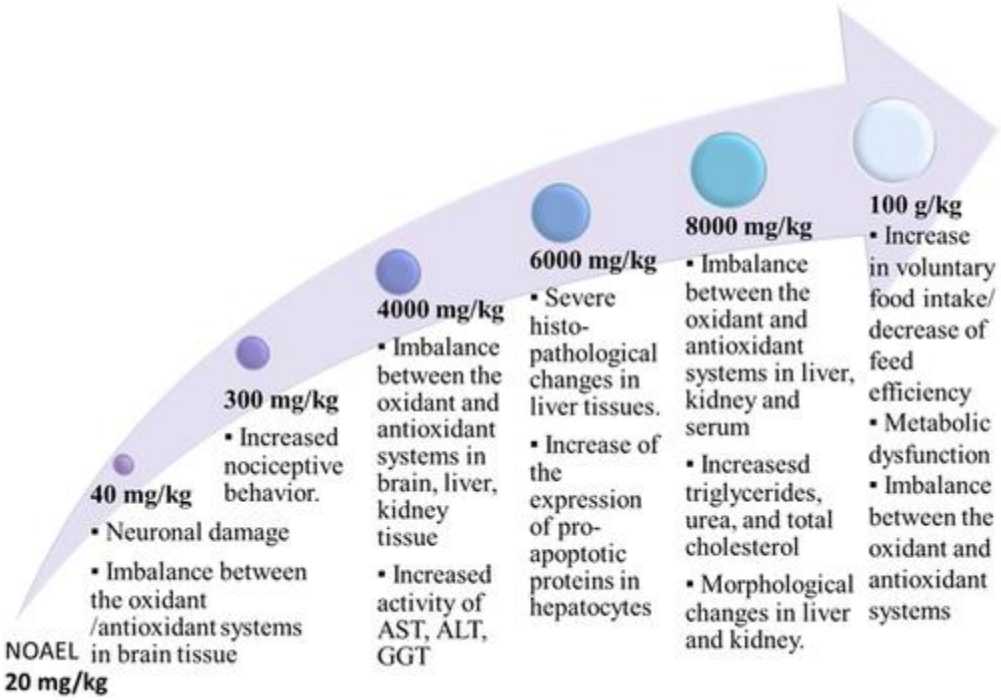


Figure E: Subchronic exposure in adult rodents—oral administration.
NOAEL, no-observed-effects level; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase.

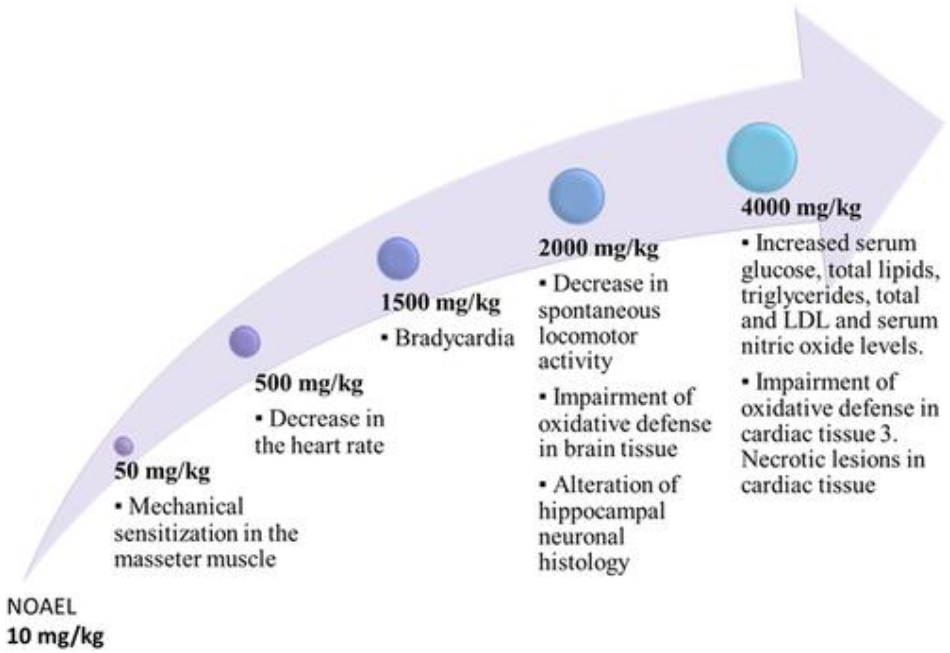


Figure F: Acute exposure in adult rodents—parenteral administration.

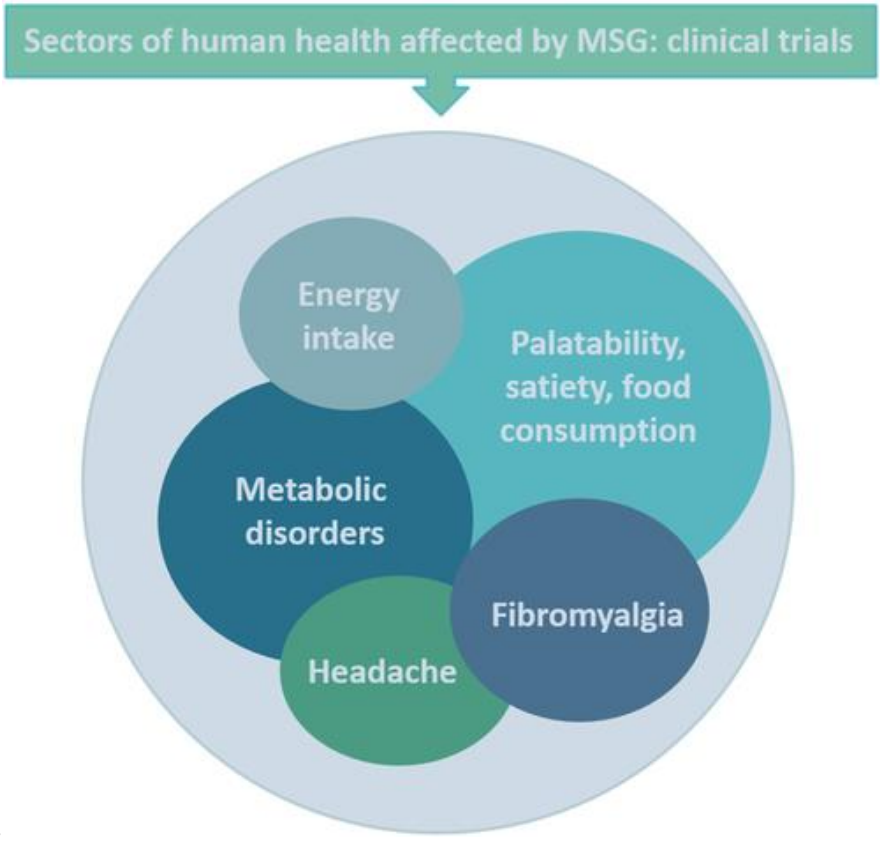


Figure G: Clinical trials reported the effects of monosodium glutamate.

Reports on MSG hypersensitivity. Furthermore, MSG was considered a possible trigger agent for some types of pain, including headache and fibromyalgia-associated pain.

Effects on the cardiovascular system

Four studies regarding MSG cardiovascular toxicity were identified. These indicated that MSG administration increased cardiac tissue oxidative stress and also determined biochemical changes, namely increasing some heart disease biomarkers, such as lactate dehydrogenase (LDH), aspartate transaminase (AST), and alanine transaminase (ALT) **(Kumar and Bhandari)** [30]. Doses between 0.5 and 1.5 g/kg induced changes in cardiac rhythm, as well as lethal tachyarrhythmia in myocardial infarcted rats (**Liu *et al*.)** [31].

Evaluation of hepatotoxicity

Several studies reported hepatotoxic effects following MSG administration. Dilatations of the central hepatic vein, with lysed erythrocytes and distorted hepatocytes, possibly due to impaired membrane permeability, were reported in adult Wistar rats, following controlled feeding with a mixture of food containing 0.04 and 0.08 g/kg MSG, daily for 42 days. Furthermore, similar results were reported in an adult male *Rattus norvegicus* study, when MSG was given with food, but at a much higher daily dose of 6 g/kg. We carefully reviewed the hepatotoxic effects reported for the 0.04 and 0.08 g/kg doses, as they were extremely low, and found that the authors justified the employed dosages based on previous work**.** [32].

MSG administration was associated with increased hepatic lipid peroxidation, reduced GSH levels, and decreased catalase (CAT) and superoxide dismutase (SOD) activity. Reports of diabetes and obesity, accompanied by steatosis, inflammation, and infiltration of lymphocytes, monocytes, and macrophages, with fibrosis and neoplastic alterations, nodular lesions, and deterioration of bile ducts, were also found. Moreover, it was reported that orally administered MSG determined an increase of liver oxidative stress at a dose that extrapolated for humans would be 0.6 mg/kg **(Paul *et al*)** [33].

Discussion:

Monosodium Glutamate (MSG) is one of the most widely used food additives although its hazard common effects. The present review highlights the effects of MSG-induced pulmonary toxicity by assessing its histopathological and histochemical parameters.

Overdosage of MSG commonly produces obesity, metabolic disorder, female infertility, and numerous undesirable symptoms in humans [34]Even the US Food and Drug Administration (FDA) and the Federation of American Societies for Experimental Biology (FASEB) did not discount the presence of a sensitive subpopulation, they affirmed the safety of MSG at levels normally consumed by the general population and concluded that there is no evidence regarding MSG food use and serious, long term medical problems. Several studies were carried out to study the toxicity of MSG on various organs in laboratory animals. MSG is reported to produce neurotoxicity [35], cardiotoxicity [36] reproductive organ toxicities [37,38] retinal damage of the eye [39], obesity and metabolic disorders[40], hepatotoxicity, and nephrotoxicity. [41]

In most recent studies, MSG treatment of mice induced many dystrophic histopathological changes in the lung tissues represented by extensive tissue damage, narrow alveolar sacs with highly thickened alveolar septae, alveolar hemorrhage, severely damaged bronchioles, cellular infiltration, and highly thickened and congested blood vessels with hemolyzed blood cells and in the lung tissues, in addition, increased PAS (ve+) materials, protein content Amyloid accumulation and decreased DNA content tissues.

Such severe histopathological changes with MSG treatment may be due to oxidative stress and subsequent overproduction of reactive oxygen species (ROS) which was postulated as the most important

mechanism of toxicity. Also, previous research reported that the increased production of reactive oxygen species (ROS) leads to pulmonary toxicity, and eventually lung fibrosis. Also, ROS has been indicated to activate profibrotic transforming growth factor-β (TGF-β) in the lung which induces the development of inflammation and induces the proliferation of the fibroblasts leading to severe pulmonary fibrosis [42]. **Katsuyama *et al***. [43] reported that ROS are generated by NADPH oxidase or mitochondrial electron transport chain in cells and are implicated in the differentiation and proliferation of cells and the stability of the genome. MSG has some harmful effects such as oxidative stress, DNA damage, protein modification, and lysis of stromal cells. [44]

These findings were explained by **Shredah[7], *et al.* and Calis *et al***. [45] who found that MSG had increased oxidative stress and inflammation in the different organ systems. It also caused glucose metabolism disorders, obesity, and coronary diseases which caused a defect in the blood circulation of all organs**.** **Kumbhare *et al***. [46] and **Hamdy *et al*** [47] *found* that there was nuclear pyknosis in all tissues treated with MSG and this may be due to DNA damage. Cellular degeneration has been reported to result in cell death, which is of two types, namely apoptotic and necrotic cell death. These two types differ morphologically and biochemically. Pathological or accidental cell death is regarded as necrotic and could result from extrinsic insults to the cell such as osmotic, thermal, toxic, and traumatic effects. Cell death in response to toxins occurs as a controlled event involving a genetic programmed in which caspase enzymes are activated.

Amyloids have been associated with the pathology of more than twenty severe human disorders since an abnormal accumulation of amyloid fibrils in organs may play a role in various neurodegenerative diseases and may lead to amyloidosis. [47] Amyloid accumulation is associated with dysfunction of mitochondria and may lead to a generation of reactive oxygen species (ROS), which can induce a signaling pathway leading to apoptosis or programmed cell death [48 49].

Prevention of MSG Toxic Effects

The studies which brought evidence about the deleterious effects of MSG administration led to further research on the potential protective effects of different molecules, especially antioxidants. Vitamin C in a dose of 100 mg/kg/day given via a metal orogastric tube simultaneously with MSG at a dose of 3 g/kg/day mixed with foods for 14 days has been shown to have a protective role against toxic nerve cell and astrocyte glial fibrillary acidic protein damage in the cerebellar cortex in male albino rats [50]. All vitamin C (200mg/kg), vitamin E (200 mg/kg) and quercetin (10 mg/kg) given personally were effective in the reduction of the MSG-induced increase in malondialdehyde, modulated glutathione levels, and glutathione-S-transferase activity and were effective in ameliorating the effects of MSG on the superoxide dismutase and catalase activity in the liver, kidney, and brain in MSG-treated rats (4 mg/g, intraperitoneally for 10 days). All antioxidants reduced MSG increase in serum alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase [51]. Similar results have been found in the study of vitamin E effects in rats fed with MSG at a dose of 0.6 mg/g by gavage. Vitamin E (0.2 mg/g) significantly reduced the lipid peroxidation, it increased the glutathione level, and decreased the hepatic activities of glutathione-stransferase, catalase, and superoxide dismutase in the liver. The activities of alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase in serum were also significantly reduced as reported by **Onyema *et al*.** [52]. Quercetin (75 mg/kg, administered in 30-day-old male Wistar rats over 42 days) has been shown to normalize HDL-cholesterol, reduce insulin, leptin, glucose and creatinine levels and increased

glutathione peroxidase and superoxide dismutase activities after MSG subcutaneous application (4 mg/g administered in neonatal rats from 2. to 12. day) [(53)]. Protective effects of pretreatment with diltiazem from the development of morphological and functional disorders in ovaries have been shown in female rat pups treated with MSG [(54)].

Conclusions:

This review showed that short-term MSG exposure caused several histopathological and histochemical changes in the different vital tissues. Therefore, MSG is considered as a toxic agent due to increased production of ROS, so that, the ingestion of this substance by humans should be reviewed and a great attention must be directed towards this substance to avoid its highly desirable uses even in small doses in our food additives and enhancers. Hence, it is necessary to conduct further studies in different animal groups, doses, and treatments to out to corroborate these findings and understand the relationship between MSG exposure and our medical problems. **The only way to prevent a reaction is to avoid foods containing MSG.**

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