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Effect of monosodium glutamate on hepatotoxicity and nephrotoxicity: A mini review

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Abstract

Seasonings are now utilised more regularly to enhance the flavour of food. Monosodium glutamate (MSG) has gained popularity in the food processing industry during the past 30 years. Numerous researches have found that MSG is a problematic substance because of the negative impact it has on both people and animals. The main focus of the present review is the toxicological effects of monosodium glutamate on body weight, biochemical parameters, hepatic and renal toxicity, and the history, chemical composition, and use of MSG as a food additive. This review's objective is to educate readers about the negative health effects of MSG.

Keywords: Monosodium glutamate; Liver; Kidney; Body weight; Biochemical parameters

1. Introduction

The demand for packaged food products has significantly increased as a result of fast lifestyle change and significant population rise. The excessive usage of food enhancers and food additives discovered in the food as a result of the high dependence on these packaged and preserved foods had deleterious effects. Genotoxicity, mutagenicity, hypersensitivity, and obesity are only a few of the negative impacts brought on by the daily use of those food additives and packaged foods. Due to their toxicity, many food additives have even been banned from usage [1].

The sodium salt of glutamic acid is called monosodium glutamate (MSG), also known as AJINOMOTO [2]. It contains 78% of glutamic acid, 22% of sodium and water [3]. MSG, often known as Chinese salt, is a chemical flavour enhancer used in a variety of foods, including processed meat, tinned food, chips, luncheon meat, crispy chicken, chicken noodles, and fast food at high-end restaurants. Numerous research revealed that MSG poses serious risks on health concerns to people [4]. It ranks among the most often used food additives in processed foods. Its use has risen throughout time, and you can now find it in a wide variety of processed goods and ingredients at any market or grocery shop. It gives processed meals with a distinctive scent known as umami in Japanese. "Savoury" is the term used to describe this flavour [5].

More than forty years ago, the phrase "Chinese restaurant syndrome" (CRS) was first used. Patients typically complain of general weakness, fatigue, palpitations, a burning sensation at the back of the neck, blistering on both arms and occasionally on the anterior thorax. These signs appear 20 minutes after eating a meal high in MSG [6]. The increase of oxidative stress is linked to the mechanism of action of MSG-induced damage to various organs, including the liver, brain, testis, and kidney [7].In rats given an intraperitoneal dose of 4 mg/g body weight of MSG, studied the possible genotoxicity of dietary MSG mediated by oxidative damage [8]. In contrast to the dramatic fall in glutathione levels caused by an increase in the activity of the glutathione-S-transferase enzyme, a significant increase in malondialdehyde (MDA) formation was seen in organs like the liver, brain, and kidney. This was a sign of elevated oxidative stress, which may have acted as a mediator in the genetically harmful effect.MSG can cause a variety of symptoms, including headache,

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chest pain, a burning feeling, and face pressure [9]. According to a study rats administered MSG had higher levels of platelets and faster bleeding and clotting time [10]. MSG has some commendable psychological and gustatory effects in addition to beneficial effects with relation to hypertension and iron deficiency [11]. However, there are also several reports of negative consequences include oxidative stress, DNA damage, protein alteration, and stromal cell lysis.

2. Chemical and physical properties of monosodium glutamate

Monosodium Glutamate (Molecular Weight: 187.13) is found to be stable when kept at room temperature for extended periods of time and is widely promoted as being white in quality or appearance. Even during routine food preparation or cooking, MSG does not disintegrate until the environment is extremely acidic (pH 2.2–2.4) or warm. It is partially dehydrated and transformed into 5-pyrrolidone-2-carboxylate at these pH values and temperatures.Furthermore, glutamate tends toracemize to D, L-glutamate at extremely high temperatures, especially under alkaline conditions. Like other amino acids, it can undergo Maillard-type reactions when reducing sugars are present. Due to its chemical features that are active in enhancing taste, MSG is known to impart a distinct flavour. It has a particular flavour because of its stereochemical structure, which includes crystalline powder in the D-isomer. It is not hygroscopic and has no distinctive flavour [12].

The range of MSG's ideal palatability concentration is between 0.2 to 0.8%, and its use typically has a self-limiting nature because excessive use decreases palatability. The highest palatable dose for people is approximately 60 mg/kg body weight [13].

2.1. Historical background

The German scientist Karl Henrich discovered and first identified MSG in the year 1866. Initially, sulphuric acid was used to treat wheat gluten in order to create glutamic acid. Professor Kikunae Ikeda of the Tokyo Imperial University in Japan succeeded in removing glutamate from the seaweed broth in 1908. Prof. Ikeda also discovered that seaweed contains brown crystals of glutamic acid that give food its distinctive flavour. But he gave this unique flavour the name "Umami." Following the filing of a patent by Professor Ikeda [14] the commercial manufacturing of MSG began in 1909.Nowadays, MSG can also be made by fermenting starch, sugar beets, sugar cane, or molasses instead of being extracted and crystallized from seaweed broth. Similar fermentation processes are used to create yoghurt, vinegar, and wine. The Kyowa Hakko Kogya firm invented the commercial L-glutamate fermentation process, and in the 1960s it switched from extracting glutamate to manufacturing it. Corynebacteriumglutamicum is employed as a microbe in the fermentation process to produce this MSG product [15].

2.2. Effect on hepatic toxicity

Due to its role in metabolism and detoxification, the liver may be adversely affected by toxic substances or their metabolites, such as MSG. Rats given MSG (0.6 mg/g body weight) for a period of 10 days start to show symptoms of liver injury. In the rat liver, lipid peroxidation (LPO) and the activities of glutathione-s-transferase (GST), catalase (CAT), and superoxide oxidase (SOD) were shown to significantly increase. Additionally, because of the increased activity of GST, the level of reduced glutathione (the substrate for GST) was lowered in the liver.It demonstrates the development of oxidative damage brought on by reactive oxygen species generation (ROS). The serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltransferase (GGT) were also increased when MSG was provided [16]. In another study, rats were given MSG at a dose of 5 mg/kg of body weight daily for 28 days showed significantly reduced blood alkaline phosphatase activity by 71.97%, but aspartate aminotransferase and alanine aminotransferase enzyme activities increased by 66.86% and 9.15%, respectively. The serum aspartate aminotransferase-to-alanine aminotransferase ratio and malondialdehyde concentration were both elevated by the treatment by a combined 287.15% and 56.59% [17].Furthermore, in another study reported that rats received MSG treatment for 14 days at doses of 0.6 and 1.6 mg/g body weight. Both the overall weight and the relative weights of the liver increased noticeably. The activity of liver enzymes including alanine aminotransferase (ALT) and γ-glutamyltransferase (GGT) increased, despite significant decrease in the levels of blood total protein, albumin, and bilirubin [18]. In another study found that consuming 6 mg/g of MSG daily for 45 days caused central vessel dilatation, severe cytoarchitectural distortions of hepatocytes, vacuumed cytoplasm, swollen mitochondria and pycnotic core vesicles, impaired endoplasmic reticulum, and a marked decrease in mucopolysaccharide content rat hepatocytes significantly expressed ki-67 and p53 pro-apoptotic proteins, together with the increase of collagen in hepatocytes and connective tissue breakdown [19]. MSG supplementation at a single dose of 4 g/kg bw/daily was given to newborn rats on days 2, 4, 6, 8, 10, 12, and 14 to raise the levels of the enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [20].The same dose of MSG caused microvesicular steatosis and inflammatory cell infiltration in the liver after five days. It also resulted in enlarged adipocytes and crown-like structures in the epididymal fat, as well as higher frequencies of monocytes and M-1 macrophages in the liver and epididymal adipose tissue [21]. Moreover, it

was reported that, mice with and without dietary restrictions were found to have higher levels of total cholesterol (TC), triglycerides (TG), low density lipoprotein(LDL), and alanine aminotransferase(ALT) when given subcutaneously administered MSG (2 g/kg bw/daily) and this resulted in significant liver steatosis. Additionally, after 6 months, the MSG-unrestricted diet group had lower total cholesterol (TC) andlow-density lipoprotein(LDL) values than the MSG-restricted diet group. While the negative effects of MSG were reversed in the 12-month period for the MSG-restricted diet group, the 12-month period for the MSG-unrestricted diet group saw the development of steatohepatitis, moderate fibrosis, and liver nodules [22].

Table 1 Effect on Hepatic Toxicity

Model Organism	Dosage	Duration	Inference	References
Male albino Wistar rats	0.6 mg/g bw	10 days	Alterations in activity of enzymes	Onyema*et al*., (2006)
Male albino rats	5 mg/kg bw	28 days	Alterations in activity of enzymes	Egbuonu*et al*., (2009)
Male and female albino rats	0.6 and 1.6 mg/g bw	14 days	Alterations in body weight and liver functions	Tawfik and Al-Badr (2012)
Male albino rats (*Rattusnorvegicus*)	6 mg/gbw	45 days	Liver injury	EL-Meghawry EL-Kenawy*et al*., (2013)
Newborn rats	4 g/kg bw	2, 4, 6, 8, 10, 12, and 14 days	Liver injury	Kumar and Bhandari, 2013
Male mice	4mg/g bw	18 weeks	Liver histopathology	Takai*et al*., 2014
Male rats	5 g/kg bw	30 days	Effects on biochemical and blood parameters	Al-Mousawi (2017)
Pregnant albino rats	7 g/10ml/kg bw	9th to 14th day of gestation	Several histological and histochemical changes in the maternal and fetal liver tissues	Eid*et al*., 2018
Rats	4 mg/kg bw	90 days	Liver steatosis	Atef*et al*., 2019
Albino Sprague Dawley rats	100 mg/kg	4 weeks	Alterations seen in liver tissues	El-Gharabawy*et al*. (2019)
Male Swiss mice	2, 4, or 8 g/kg bw	14 days	Impairs memory, motor activity and hepatic functions in mice	Omogbiya*et al*., 2021
White albino male rats	2 g/kg bw	4 weeks	Liver injury	Mohamed *et al*., (2021)
Pregnant female rats	1 g/5 mL/kg bw	0 to day 20	Several biochemical, histological, and histochemical changes in the maternal and fetal liver tissues	El-Hak*et al*., 2021

MSG at a dose of 5 g/kg bw/daily for 30 days elevated the levels of aspartate aminotransferase (AST),alanine aminotransferase (ALT), and alkaline phosphatase (ALP) in rats [23]. In a study conducted on pregnant rats, rats were divided into 2 groups: control and MSG supplementation group with a dose of 7 g/10ml/kg bw/daily from the 9th to 14th day of gestation. Then, two subgroups of the expectant moms were created; the first was dissected on the 15th day of gestation and the second on the 19th. In both maternal and foetal liver tissues, MSG supplementation led to vacuolation in hepatocytes, degenerative and necrotic regions, and atrophied size of hepatocytes with pyknotic nuclei. These alterations were visible in the portal and centrilobular zones [24].In another study MSG can harm the pathway from the hypothalamus arcuate nucleus to the paraventricular nuclei, leading to obesity, fatty liver, inflammatory cell infiltration, and fibrosis [25]. Further, the dose of 4 mg/kg bw/daily MSG supplementation increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), triglycerides(TG), and malondialdehyde (MDA) levels in rats after 90 days while lowering superoxide dismutase (SOD) and glutathione(GSH)

levels. These rats also developed steatosis, which included enhanced vacuolation, severe fibrosis, and centrilobular liver cell death. Eliminating MSG somewhat reversed pathological and metabolic alterations, but it did not bring it back to normal [26]. Similar findings were obtained in another study that treated mice with 360 mg/kg each day for a month. Mild liver architecture disturbances, small necrotic areas with mild vacuolation, an enlarged and congested central vein with disturbed endothelial lining, more lymphocytic infiltration, few inflammatory cells, and an accumulation of fat droplets were among the significant alterations seen in liver tissues treated with MSG. Most of the cellular nuclei are atrophied, with haemorrhage, regions of necrosis, and increased vacuolation [27]. In another study stated that 20 male rats were split equally into 4 groups and given MSG. Serum aspartate transaminase (AST), alanine transaminase (ALT), and alanine phosphatase (ALP) levels were significantly increased. Albumin, total protein, and salt levels in rats significantly decreased [28]. Additionally, a recent study found that consuming 2, 4, or 8 g/kg bw of MSG for 14 days enhanced the liver's cytoarchitectural integrity and hepatic enzyme activity alanine transaminase (ALT), aspartate transaminase (AST), and alanine phosphatase (ALP) [29]. In another study reported that 4 weeks of exposure to 2 g/kg bw of MSG significantly damaged the hepatic tissues, causing congestion, dilated blood vessels, and a variety of cellular alterations, including necrosis, apoptosis, polymorphism, and prominent kupffer cells [30]. According to a study, pregnant women and their foetuses who received a 1 g/5 mL/kg bw MSG supplement from day 0 to day 20 of gestation had lower superoxide dismutase (SOD) and glutathione(GSH) activity in addition to higher levels of TNF- and NO in their liver tissue [31]. These studies showed that varied doses, periods, and methods of MSG delivery resulted in modifications in hepatic morphology, liver enzymes, and antioxidant defense.

2.3. Effect on renal toxicity

According to a study MSG intake can result in oxidative stress by depleting endogenous antioxidants in the kidneys and raising reactive oxygen species (ROS), which causes the oxidation of lipids, proteins, DNA, and RNA as well as cellular damage [32,33]. Also, they noted that supplementing with 4 g/kg bw/daily MSG for 10 days increased lipid peroxidation and lowered glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) levels in the kidney. Additionally, it led to a considerable increase in blood sugar and kidney glucose concentration as well as a decrease in the activity of glucose-6-phosphate dehydrogenase [32]. A similar study found that MSG supplementation (4 g/kg bw/daily for 180 days) significantly increased kidney function parameters (urea, uric acid, and creatinine), lipid peroxidation markers malondialdehyde (MDA) and conjugated dienes and altered the antioxidant system superoxide dismutase(SOD),catalase(CAT), glutathione peroxidase, glutathione transferase, and reduced glutathione. In the kidney, it was possible to see swollen tubules, congested capillaries, and microhemorrhages in the tubular stroma [33]. Furthermore, rats treated with MSG for 10 days at a dose of 4g/kg body weight showed an increase in glucose 6-phosphatase (G6Pase) activity, a decrease in glucose-6-phosphate dehydrogenase (G6PD) activity, and a significant alteration in several oxidative stress parameters as well as in the accumulation of glucose in the blood and kidneys [34]. MSG at a dose of 2 mg/g bw/daily in drinking water for 9 months increased the risk of kidney stones forming and caused urine to become more alkaline. Moreover, MSG treatment raised blood creatinine and potassium levels, as well as urine output volume, urinary sodium, citrate excretion, decreased ammonium, magnesium excretion, and caused 20% of the rats to develop hydronephrosis [35]. According to a study on the nephrotoxicity of MSG supplementation at a dose of 5 g/kg bw/daily for 30 days elevated serum urea and creatinine levels and adversely affected renal functions in rats [36]. In another study MSG treatment caused renal failure and a considerable rise in body weight in experimental animal models[37].

In another study explained that albino mice treated with MSG. Significant changes in the weight and volume of the kidneys were observed in the gross morphology, while the urine space was significantly enlarged, the proximal convoluted tubule (PCT) and distal convoluted tubule (DCT) were dilated, and the lining cells of the PCT and DCT lost their luminal microvilli [38]. Like this, a recent study discovered that different MSG doses (500 mg/kg, 750 mg/kg, 1000 mg/kg, and 1250 mg/kg bw for 8 weeks) increased the amounts of creatinine, urea, total bilirubin, conjugated bilirubin, and unconjugated bilirubin [39]. Additionally, rats exposed to 3 g/kg bw of MSG for 6 months had significantly higher serum levels of malondialdehyde(MDA), blood urea nitrogen(BUN), creatinine, uric acid, and Caspase-9, NGAL, and KIM-1 [40]. In addition, rats exposed to 15 mg/kg bw of MSG for 30 and 60 days developed mesangial proliferative glomerulonephritis due to an expansion in a mesangial mass characterised by mesangial cell hypertrophy and hyperplasia [41]. According to a study rats given MSG at a variety of doses for 30 days had higher urea-creatinine blood concentrations [42]. In another study reported that adult Wistar albino rats were given MSG for 21 days, which resulted in a significant increase in the levels of lipid peroxides (LPO), glutathione-S-transferase activity, and total antioxidant capacity, as well as a decrease in the activity of superoxide dismutase. Histopathological lesions caused by MSG included fibrosis, decreased glycoprotein content, and a rise in the number of apoptotic cells [43]. These studies showed that MSG intake has a negative impact on kidney function measures, kidney morphology, kidney histology, and antioxidant defense.

Table 2 Effect on Renal toxicity

Model Organism	Dosage	Duration	Inference	References
Rats	4 g/kg bw	10 days	Cellular damage	Okwudiri and Paul (2012)
Rats	4 g/kg bw	10 days	Accumulation of glucose in the blood and kidneys	Onyema*et al*., 2012
Rats	2 mg/g bw	9 months	Increased the risk of kidney stones	Sharma *et al*., 2013
Male rats	5 g/kg bw	30 days	Elevated serum urea and creatinine levels	Al-Mousawi, 2017
Sprague–dawley male albino rats	35 mg/kg/d	2 weeks	Alterations in the body weight and kidney functions	Elbassuoni*et al*., (2018)
Neonatal Albino mice	2 mg/g bw	75 days	Significant changes in the weight and volume of the kidneys	Bhattacharya and Ghosh, 2019
Male Wistar rats	500 mg/kg, 750 mg/kg, 1000 mg/kg, and 1250 mg/kg bw	8 weeks	Increased the amounts of creatinine, urea and total bilirubin	Airaodion*et al*., 2020
Male sprague-dawley rats	3 g/kg bw	6 months	Renal histopathological changes	Koohpeyma*et al*., 2021
Rats	15 mg/kg bw	30 and 60 days	Mesangial cell hypertrophy and hyperplasia	Hussin*et al*., 2021
Rats	Different doses of MSG	30 days	Higher urea-creatinine blood concentrations	Alhamed*et al*., (2021)
Wistar albino rats	30 g/ kg bw	21 days	Histopathological lesions caused by MSG	Abd-Elkareem*et al*., (2022)

3. Conclusion

It was concluded that MSG was found to be used as a flavour enhancer in many different food industries and regular household settings. It surely has a pleasant flavour and makes you want to eat more, especially in those who are experiencing appetite loss. Because it has toxic effects on hepatic and renal functions, changes in body weight and biochemical parameters, MSG is a major caustic effective agent against human health. More people should be made aware of MSG's negative effects, and they should be advised to choose natural MSG alternatives.

Compliance with ethical standards

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No conflict of interest to be disclosed.

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