Review Article

# Genotoxicity of Monosodium Glutamate: A Review on its Causes, Consequences and Prevention

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## ABSTRACT

Monosodium Glutamate (MSG) is a common food additive used in processed foods to enhance the taste. The data available on Google scholar, NCBI, PUBMED, EMBASE, Wang fang databases, meta-analysis and Web of Science were reviewed to collect the information on the MSG-induced genetic damages, consequences and its mechanism. The retrieved information indicated that long-term consumption of MSG is associated with metabolic diseases, neurological and reproductive organ defects. Studies also suggested that MSG has the ability to induce genotoxicity. The damages on the genes have the tendency to implicate several diseased states in the host, not only in the present generation but also in the progeny. Considering the consequences of genetic damages on the population, this review was done to find the mutagenic potential of MSG, its causes and the preventive strategy for reducing the MSG-mediated genetic defects.

**Key words:** Monosodium glutamate, Food additive, Genotoxicity, Oxidative stress, Antimutagens.

## INTRODUCTION

Monosodium glutamate is probably one of most frequently used additive in the food industry as a taste enhancer. It was in 1908, a scientist by name Ikeda discovered the taste of glutamate found in seaweeds. MSG can be extracted from molasses by fermentation of beet sugar, sugar cane, starch and corn sugar. MSG is commonly referred as 'Ajinomoto / Chinese salt' and is added in chips, jelly, pastry, candy, pizza, noodles and even protein-rich food products like meat, fish, milk and some vegetables.[1] MSG is known to produce a type of flavour which the Japanese describe as 'umami' or 'savory'. It has been estimated that at an average in an industrialized country, a person consumes about 0.3 to 1.0 gm of MSG per day.[2] Glutamate is considered to be one of most richly found amino acid in the body and is also richly present in natural food substances that contain proteins. Glutamate is a known excitatory neurotransmitter in central nervous system that acts through ionotropic (iGluR) and metabotropic (mGluR) glutamate receptors. The glutamate bound to protein has no taste-enhancing effect and its disintegration takes place only in the small intestine. Studies have indicated that glutamate exhibits its action by binding to its specific receptors located in the taste bunds and stomach and innervations takes place through gastric vagus nerve.[3]

The actions of MSG has been commonly referred as 'Chinese Restaurant Syndrome' and are characterized by headache, flushing, sweating, numbness / burning sensation in mouth and throat, nausea and fatigue. Although these symptoms are reported to vary depending on the concentration and duration of exposure but chronic use of MSG has been linked to several pathological conditions.[4]

Long-term consumption of MSG is reported to cause several health complications such as;

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- Metabolic diseases – Diabetes, dyslipidemia, obesity.[5]
- Cardiovascular disease – Hypertension, heart ailments.[6]
- Sleep-breathing and respiratory disorder – Apnea, sleep disturbance.[7]
- Neuro-endocrine defects – Depression, anxiety.[8]
- Reproductive system damages – Alterations in the size and shape of reproductive organs, diminished testosterone levels.[9,10]
- Liver diseases – Hepatitis, elevation in the marker enzymes for liver damage.[11]
- Allergic reactions – Dermatitis, itching, rashes, urticaria, cracked skin.[12]

Clinical case studies have also indicated that MSG exposure increased the perception for pain stimulus and complicated the symptoms in both asthmatic and non-asthmatic patients.[13,14] Apart from these, MSG exposure is reported to induce damages in the nuclear organization of the host cells leading to genotoxicity.[15-17] Genetic damages on the host cell is reported to have the tendency to produce mutations. The changes on the genetic set-up if not corrected can lead to health ailments, neurological defects, metabolic diseases and cancer.[18] The studies to determine the genetic potential of the compound assumes its importance since the defects not only occur in the present generation but also can be inherited to the progeny.[19] Considering the information on MSG, this review was planned to determine the causes, consequences and prevention of MSG-mediated genotoxicity on the host cells.

## Genotoxicity testing

'Genotoxicity' refers to ability of a substance to cause adverse effects to the genetic component of the cell (DNA, RNA). If the genetic make of the cell is permanently altered leading to heritable defects then it is called as mutation. All genotoxins could be mutagenic in nature. There are various causes for mutation such as exposure to environmental pollutants, occupational exposure to chemical mutagens, radiation, certain medication and viral infection. Mutagens induce damage to the nuclear components by multiple pathways such as direct attack on nucleus, indirectly by producing chemical metabolite that has affinity to DNA, by increasing the production of free radicals.[20] The consequence of genotoxicity is represented in Figure 1.

The genetic damages results into various diseases, some manifested in the present generation (somatic cell damages) and some will be seen in the progeny (germinal cell damages). Cancer, heart diseases, neurological defects are some of the examples of somatic cell mutation while sickle cell anaemia, cystic fibrosis are categorized under germinal cell nuclear defects.[21] There are several *in-vitro* and *in-vivo* tests available to detect the ability of a compound to induce genetic damage. In these assays, the test compound will be exposed at a predetermined dose and duration by a suitable route of administration to the isolated cells or the whole animals and damages induced to the nuclear component will be measured. Some of commonly employed test methods are as follows;[22]

*In-vitro* methods

- Ames test
- Mouse lymphoma TK assay
- Chromosomal aberrations test

*In-vivo* methods

- Bone marrow micronucleus test
- Comet assay
- Transgenic assay

## *In-vitro* mutagenic studies for MSG

An *in-vitro* test on the mitotic index and genotoxicity of MSG was tested in *Vicia faba* seedlings and the data showed that MSG dose at 10 g/L inhibited the cell division and caused a reduction in mitotic index and additionally produced an increase in the genomic template stability tested by using RAPD-PCR. The analysis indicated that MSG has significant genotoxic potential and also reduce the seed germination property in *V. faba*.[23]

In this study, *Allium cepa* assay was used to evaluate the genotoxic and cytotoxic potential of MSG. The root tips of onion were exposed to four concentrations of MSG (1, 3, 5 and 7 g/L) dissolved in distilled water. Macroscopic (morphology and colour of roots) and microscopic (mitotic index and chromosomal aberrations) examinations were done on the root tips. The analysis of the results indicated that the tested doses of MSG reduced the growth of roots and changed the color of root tips from normal pink color to brownish / black colour. MSG also induced chromosomal aberration at telophase and reduced (non-significantly) the mitotic index.[24]

In a similar study, MSG tested on *Allium cepa* produced significant chromosome aberrations like bridges, fragments, disturbance, sticky chromosomes and other morphological abnormalities like enlargement of cells in root tips.[25] One more research on onion root tip indicated a reduction in mitotic index besides chromosomal damage with MSG.[22] Also in another findings, the data on the study in onion root tip suggested both chromosomal damage and reduced mitotic index.[26] The results

suggested that MSG has the potential to induce both genotoxicity as well as cytotoxicity in *Allium cepa*[24-26]

The genotoxic potential of MSG was evaluated by chromosome aberrations (CAs), sister-chromatid exchanges (SCEs), cytokinesis-blocked micronucleus (CBMN) and random amplified polymorphic DNA-polymerase chain reaction (RAPD-PCR) in cultured human lymphocytes and alkaline comet assays in isolated human lymphocytes. The studies were done using six concentrations of MSG viz., 250, 500, 1000, 2000, 4000 and 8000 μg/mL. The observation of the study indicated that MSG significantly and in a dose-dependent manner increased the frequencies of CAs, SCEs and MN. The RAPD-PCR test suggested both increase and decrease in band intensity and gain or loss of bands and the comet assay revealed significant DNA damage. The results indicated that MSG might possess the genotoxic potential in the isolated human peripheral lymphocytes.[27]

### *In-vivo* mutagenic studies for MSG

The study on the Drosophila melanogaster indicated that MSG exposure produced changes in the wing development due to the action of MSG on the integrity of chromosome and transcription of genes. The results suggest that MSG can produce new mutation which is recessive in its action and has the potential to alter phenotype in Drosophila.[28]

The genotoxic effect of MSG was tested at 4 mg/g body weight using the rat bone marrow micronucleus test. The data indicated that administration of MSG significantly increased the formation of micronucleated polychromatic erythrocytes besides increasing the oxidative stress compared to the control groups. This study was done to evaluate the influence of dietary antioxidant such as vitamin C, vitamin E and quercetin in the MSG-induced oxidative damage to organs such as liver, kidney and brain in rats. The results suggested that antioxidant potential of a compound can reduce the number of micron cleated erythrocytes and toxic manifestations on organs.[29]

The ability of MSG to induce genotoxicity in palatal mucosa was studied in adult albino rats. MSG was tested at 20 and 40 mg/kg for two months and then palatal samples were isolated. The samples were stained with haematoxylin and eosin stains and the histological examination revealed papillary fold projections, bulbous shape rete pegs (epithelial cell projections in connective tissues) in the basal cell layer of oral epithelium. The molecular study indicated reduction in DNA quality and quantity in these cells compared to the control group. The study concludes that MSG has genotoxic effects on the palatal mucosa of rats.[30]

A study done to evaluate the protective effect of *Moringa* leaf extract against the MSG induced cellular and nuclear damages in rats indicated that administration of MSG (5 mg/kg) produced significant DNA damage besides increasing the PCNA and p53 expressions compared to the untreated group. These effects were related to the oxidative potential of MSG where it not only produced organ level damage but also induced significant genotoxicity. The observation suggests that *Moringa* leaf extract due to its antioxidant property has the potential to reduce the nuclear-defect complications of MSG.[15]

The study conducted to find the influence of MSG on the markers of genotoxicity indicated that when adult male Sprague dawley rats were treated with MSG, a significant increase in expression of gadd45b (Growth Arrest and DNA Damage Inducible Beta) marker was observed. The treatment also dose-dependently increased the IL-8 and Bax and reduced the Bcl-2 levels. An increase in the biomarkers for the liver damage was also observed. The authors concluded that MSG-induced genotoxicity could be mediated through expression of gadd45b gene that has an influence on the cell growth and death program signalling mechanism and MSG-mediated liver toxicity has tendency to show more complications in patient with pre-existing hepatic diseases.[16]

A study to evaluate the modulatory effect of *Chlorella vulgaris* and *Spirulina platensis* against the MSG induced genotoxicity and apoptosis indicated that MSG increased DNA fragmentation and apoptosis. The finding showed that MSG up regulated the mRNA Bax, caspase-3 genes, down-regulating Bcl-2 gene expression besides inducing significant oxidative stress and hepatic cell damage.[17]

### Mechanism suggested for MSG-induced genotoxicity

The mechanism reported for MSG-induced genotoxicity is both direct as well as indirect attack on the nucleus. In the direct attack, the data from the earlier studies indicated that MSG induced significant chromosomal aberrations, clumping and stickiness of chromosomes in the anaphase. The stickiness of chromosomes can occur due to disturbances in protein adhesion or DNA / RNA metabolism. The study also indicated that MSG can inhibit the spindle fibre and can influence the separation of anaphase.[31]

The nuclear fragments observed in *in-vivo* micronucleus and comet test also suggests the direct nuclear damages. Micronucleus is the left-over part of main nucleus in the cytoplasm after the nuclear injury. During erythropoiesis, the main nucleus will get expelled out; however the damage part will remain as micronuclei.[29] The comet

assay indicates the extent of damage to the nuclear part of the cell has undergone. If there is a large fraction is left behind as an extended tail, it is an indicative of severity of DNA damage. The observation from MSG study indicated an increase in the DNA tail length (TL), DNA tail intensity (TI) and DNA tail moment (TM).[16] MSG also reported to increase the DNA breaking number, making the super-coiled loops of DNA to relax more and cause large fraction of DNA to move.[32] These studies suggested the ability of MSG to induce nuclear damage in the host cells.

In the indirect mechanism, MSG is found to enhance the oxidative stress as well deplete the antioxidant defence enzymes such as superoxide dismutase, catalase and glutathione peroxidase in the host.[33] The markers of oxidative stress were indicated by the elevation in the level of malondialdehyde (MDA) and Xanthine Oxidase (XO). Lipid peroxidation in cell membrane induces structural changes in the polyunsaturated fatty acids which are essential for normal functioning of the cells. MDA is considered to be final end-product of lipid peroxidation of ROS.[34]

On the other hand, XO catalyses the conversion of hypoxanthine to xanthine and then to uric acid. In normal condition it does not contribute in free radical generation. However, in pathological states, XO can catalyse the reduction of oxygen to form superoxide anions and hydrogen peroxide contributing in oxidative stress.[35] It is reported that due to alteration in oxidative-antioxidant balance, the accumulated ROS will now start attacking the host cellular components such as DNA, lipids and proteins leading to alterations in the biological functions, mutations and apoptosis.[36,37]

Oxidative stress due to reactive oxygen species is known to cause apoptosis. The programmed cell death / apoptosis is the normal physiological response shown by most multi-cellular organism. The response occurs to ageing, cell injury and can be triggered by several factors such as oxidative stress. It was reported earlier that MSG administration induces apoptosis by causing the down-regulation of Bcl-2 protein in thymus glands.[38] According to Rezzani *et al.* (2003) the glutamate induced apoptosis can be related to the activation of mGluR5 receptors leading to increased intracellular $Ca^{2+}$. The abnormally increased $Ca^{2+}$ results in excessive uptake of $Ca^{2+}$ into the mitochondria which then starts the cell death mechanisms by releasing the pro-apoptotic factors in the cytosol such as procaspase, cytochrome C, apoptosis-inducing factor, apoptosis protease-activating factor 1 and, ultimately activates caspases to execute the cellular death. Calcium-mediated activation also reported to cause the generation of free radicals such as superoxide anions.[39]

Studies also indicated that MSG treatment significantly down-regulated and up-regulated the Bcl-2 and Bax proteins level in the liver homogenate, respectively. Bcl-2 are referred as anti-apoptotic proteins and its pro-apoptotic partner is Bax. The family of Bcl-2 proteins are confined to a small area on the cytoplasmic face of the mitochondrial outer membrane, endoplasmic reticulum and nuclear envelope, maintains the mitochondrial membrane integrity by preventing the release of cytochrome c which, together with APAF-1, facilitates the activation of caspase-9.[40]

In comparison, the pro-apoptotic Bax, identified as an inhibitory binding partner of Bcl-2, is activated in response to genotoxic stress, causing conformational changes, membrane-insertion and oligomerization to shape a channel in the mitochondrial outer membrane, through which cytochrome C exits to the cytosol to trigger caspase-9, initiating the caspase cascade activation and hence cell death (Figure 2). Further, the homodimer formation ability of Bax is considered as the dominant regulator of the cell death signal. The Bax/Bax homodi-

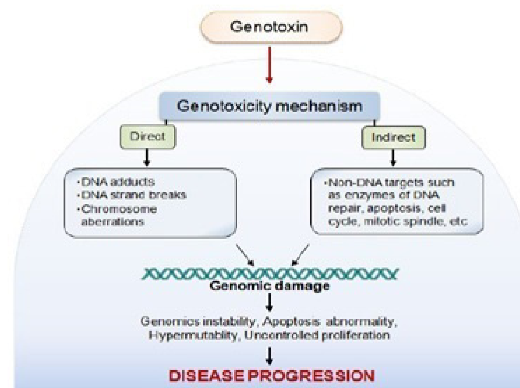


**Figure 1: Schematic representation of genotoxicity and its progression to disease condition.[20]**

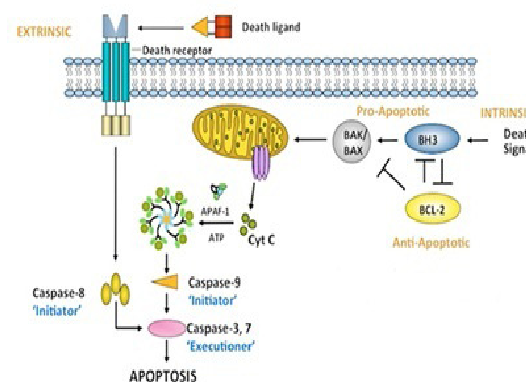


**Figure 2: Schematic representation to indicate the molecular mechanism of apoptosis.[40-42]**

mer formation can antagonize the anti-apoptotic function of the Bcl-2 protein, leading to cytochrome C liberation and apoptosis initiation.[41]

MSG has been reported to elicits the response of stress genes called gadd45 (growth arrest and DNA damage inducible 45). The genes are concerned in cell cycle arrest, DNA repair and apoptosis. The expression of the gene is inducible due to different types of stress including oxidative and genotoxic.[42] In addition to this, MSG has been reported to the trigger several pro-inflammatory mediators such as interleukin-8, nuclear transcription factor-kappa B (NF-kB), Tumor necrosis factor (TNF-α).[31,43]

Gadd45b is considered to be a pro-apoptotic and growth-arresting protein and executes these actions depending on the nature and strength of the stress. In mammalian cells, the response of this gene is considered to maintain the cellular genomic integrity by averting the fixation of permanent damage from genotoxic stress. The function of the gene involves activation of cell cycle arrest at G1/S and G2/M transitions and activation of the cell death program depending on the extent of damage. The study suggests that MSG exposure triggered apoptosis rather than DNA repair.[40] Enhanced apoptosis is also considered as a marker of genotoxicity.[43,44]

Studies also indicated that MSG exposure increases the expression of PCNA and p53 in rats. These are the biomarkers reported for the cell proliferation and apoptosis.[45] Studies further suggested that MSG has the potential to suppress the tumor suppressive genes.[46]

Based on these information, the genotoxic mechanism of MSG can be summarized as;

- Direct attack on the nuclear components of the cells.
- Enhancing the oxidative stress by increasing the production of ROS and reducing the antioxidant enzymes.
- ROS mediated cellular damage leading to apoptosis and mutations.
- Inhibition in the action of tumor suppressive genes.
- Triggering the release of mediators for inflammation and cell proliferation.

## MSG and carcinogenicity

Studies conducted in the past reported that MSG administration is associated with carcinogenesis. In one such study, it was observed that MSG-induced obesity caused steatosis and steatohepatitis, resembling the pre-neoplastic lesions that were commonly seen in human non-alcoholic fatty liver disease. The cellular hyper-excitability involving the sodium gated-voltage channels and ligand excitatory glutamate as well the increased oxidative stress are reported to be important risk-factors for these pre-neoplastic lesions.[47]

In another study, new born mice treated with MSG (2 mg/g, s.c., for 4 days) produced several obesity-related parameters such as hyperinsulinemia, hypercholesteremia and hyperglycemia. The study further indicated that animals tested with MSG had shown more tendencies to develop the colorectal cancer.[48] The findings suggested that metabolic programming of several types of cancer cells got altered after MSG exposure. Glutamine present in the body plays an important role in getting converted to glutamate by glutaminase tumours and is involved in the synthesis of ATP. This process reported to regulate the energy consumption in the cancer cells.[49]

Studies have indicated that obesity being a major complication of MSG has the tendency to amplify the incidences of carcinogenicity. In addition to the mechanism discussed already, the pathways also include the activation of insulin-IR-ERK1/2 and modulation of anti-apoptotic action of immune cells.[50] However, some researchers have indicated that these conditions do not normally mimic in human and have little relevance for human tumorigenesis.[51]

## Strategies for preventing the MSG-mediated genotoxicity

Since it is inevitable to avoid the exposure to food additives such as MSG, the best way to minimize their effects is by increasing the use of substances that possess ant mutagenic potential. There are several examples of substances (both synthetic and natural) reported in literature where the compounds exhibited ant mutagenic property.

Their mechanisms of ant mutagenesis include;[51,53]

- Direct inactivation of mutagen
- Increasing the antioxidant status
- Inhibiting the conversion to active mutagens
- Increasing the level of metabolizing enzymes
- Rapid elimination from host system.

The compounds that are reported to possess the ant mutagenic property against the MSG are *Origanum majorana, Ruta chalepensis, Vicia faba, Moringa oleifera, Chlorella vulgaris* and *Spirulina platensis*. And the most common mechanism reported for the ant mutagenesis is the antioxidant effect of the natural substance.[15,16,23]

From the data discussed, it can be noted that generation of ROS plays an important role in the mutagenesis; their prevention is reported to be an important strategy for the ant mutagenesis. The compounds that exhibited antioxidant activity has been reported to

reduce the interaction of ROS with targets in the DNA, increased the level of protective enzymes such as SOD, CAT, GSH-Px, augmented the DNA repair / synthesis mechanism.[54]

## CONCLUSION

Monosodium glutamate extensively used in food industry has been tested for genotoxic potential in the *in-vitro* and *in-vivo* tests. The data from this review suggested that MSG has the potential to induce the nuclear damages in the host cells. The available information indicated that MSG could produce genetic damages both by direct as well as indirect mechanisms. In the direct action, MSG can induce chromosomal aberrations, clumping and stickiness of chromosomes, besides inhibiting the spindle fibre in the anaphase. The indirect effect of MSG is mediated through the generation of oxidative stress in the host cells. The reactive free radicals have the ability to cause direct effect on the nuclear component of cells besides, inducing structural and functional defects in the genes. Molecular mechanisms such as alterations of Bcl-2, Bax protein, gadd45, NF-kB, TNF-α and p53 levels have also been linked to the genotoxic effects of MSG. Alterations in the genes if not corrected can leads to several diseased states not only in the present generation but also in the offspring.

Enhancing the host defence mechanisms is one of the most effective strategy to counteract against the deleterious effects of environmental mutagens and carcinogens that accidently or intentionally enter our host system. Increasing the use of natural ant mutagens in the diet has the tendency to increase the host anti-mutagenic mechanisms that will effectually provide protection against genotoxic complications of substances that are difficult to avoid in our daily life.

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None.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

## ABBREVIATIONS

**MSG:** Monosodium glutamate; **iGluR:** Inotropic glutamate receptors; **mGluR:** Metabotropic glutamate receptors; **RAPD-PCR:** Random amplified polymorphic DNA-polymerase chain reaction; **CAs:** Chromosome aberrations; **CBMN:** Cytokines blocked micronucleus; **SCEs:** Sister Chromatid exchanges; **MN:** Micronucleus; **PCNA:** Proliferating cell nucleus antigen; **ILs:** Interleukins; **Bcl-2:** B cell lymphoma-2; **Bax:** Bcl-2 associated X protein; **TL:** Tail length (DNA); **TI:** Tail intensity (DNA); **TM:** Tail moment (DNA); **XO:** Xanthine oxidase; **MDA:** Malondialdehyde; **ROS:** Reactive oxygen species; **NF-kB:** Nuclear transcription factor kappa-B; **TNF:** Tumor necrosis factor; **SOD:** Superoxide dismutase; **CAT:** Catalase; **GSH-Px:** Glutathione peroxidise.

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## PICTORIAL ABSTRACT