Understanding the toxicity of Monosodium glutamate and natural protective strategies to mitigate: A comprehensive review

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ABSTRACT

Monosodium glutamate is a sodium salt of a nonessential amino acid, L-glutamic acid, which is widely used in food industry. Glutamate plays an important role in principal brain functions including formation and stabilization of synapses, memory, cognition, learning, as well as cellular metabolism. However, ingestion of foodstuffs rich in monosodium glutamate can result in the outbreak of several health disorders such as neurotoxicity, hepatotoxicity, obesity and diabetes. The usage of medicinal plants and their natural products as a therapy against MSG used in food industry has been suggested to be protective. Calendula officinalis, Curcuma longa, Green Tea, Ginkgo biloba and vitamins are some of the main natural products with protective effect against mentioned monosodium glutamate toxicity through different mechanisms. This review provides a summary on the toxicity of monosodium glutamate and the protective effects of natural products against monosodium glutamate -induced toxicity.

Keywords: Monosodium Glutamate, toxicity studies, Protective effects

1. INTRODUCTION

Monosodium Glutamate (MSG) was discovered in 1908 by Professor Kikunae Ikeda, a Japanese chemist at Tokyo Imperial University, who had been working to isolate the ingredient that gave a particular taste in kombu (a Japanese seaweed), who has identified natural flavor enhancing substances from seaweed. Monosodium glutamate (MSG) is one of the world's most widely used food additives and flavor enhancer, MSG increases the sappiness of food. MSG produces a flavor that cannot be provided by other food products. Monosodium glutamate belongs to the larger group of chemicals that are labeled "glutamate." Glutamate is one of many different amino acids, which are considered to be the building blocks of proteins. Glutamate itself is regarded as one of the most important components in proteins [1]. In fact, it is found naturally in many protein-containing foods, including cheese, milk, meat, fish and a number of different vegetables. The levels of MSG are particularly high in foods like tomatoes, mushrooms and Parmesan cheese. Glutamate is a key component in determining the flavor of these foods, however it only functions as an enhancer when it is in its "free" form, not when it is bound with

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other amino acids in proteins. MSG, is one of the most common and easily available food additives in food Industry. It is used for the maintaining freshness, flavor, taste, texture, or appearance of food and also used for preservation like salt, (in meats such as bacon or dried fish), sulfur dioxide (in wine), or sugar (in marmalade). Additives also ensure the processed food items to be in good condition [2]. Use of a food additive is justified only when it retains the nutritional value of the food and does not cause any harm to health when consumed in due course of time. Which are nonnutritive substances added to food in small quantities, to improve appearance, flavor, texture or storage properties. Above the 3,000 different chemical compounds are used as food additives [3]. They are classified into different groups, such as Antioxidants, Chelating Agents, Coloring Agents, Curing Agents, Emulsifiers and *Flavors and Flavor Enhancers*. Monosodium glutamate is one of the flavoring agents and Flavor additives. Which is naturally occurring and added to food gives the characteristic flavor to almost all foods in our diet. Flavor enhancers are not flavors but they amplify the flavors of other substances through a synergistic effect. Flavor and flavor enhancers constitute the largest class of food additives. Natural flavor substances, such as spices, herbs, roots, essences, and essential oils, have been used in the past as flavor additives. The flavors are in short supply and the amount of flavour substances in them is very tiny [4]. It would take about a ton of many spices to produce 1 g of the flavor substances, and in some cases only 0.1 g can be extracted. Natural food flavors are thus being replaced by synthetic flavor materials. The agents responsible for flavor are esters, aldehydes, ketones, alcohols, and ethers. These substances are easily synthesized and can be easily substituted for natural ones [5]. Typical of the synthetic flavor additives are amyl acetate for banana, methyl anthranilate for grapes, ethyl butyrate for pineapple, etc. Generally, most synthetic flavors are mixtures of a number of different substances. For example, one imitation cherry flavor contains fifteen different esters, alcohols, and aldehydes [6]. Figure 1.

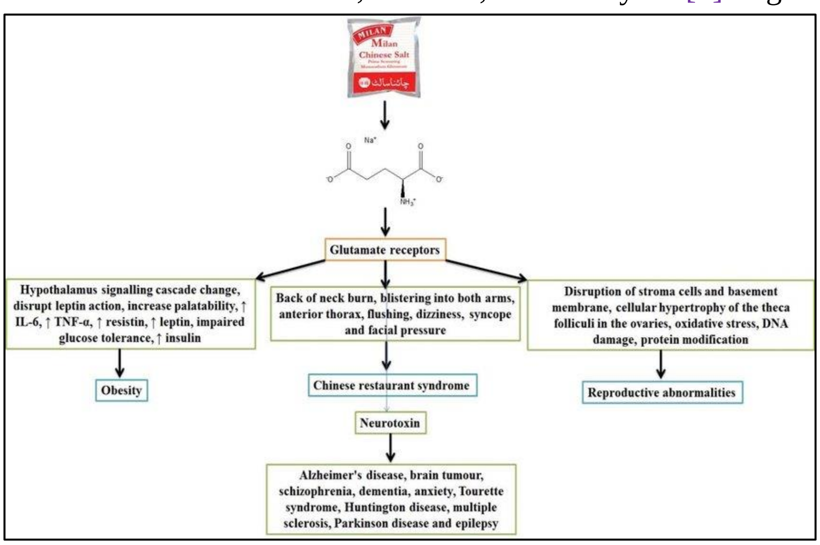

Figure 1. MSG toxicity leads to different disorders

2. Search strategy

This comprehensive review was performed by searching in Scopus, Web of Science, PubMed and Google Scholar to identify all published articles about the chemistry, toxicity of MSG, and protective effect of natural products against MSG from their inception up to August 2022. The search terms included “monosodium glutamate”, “toxicity”, “nephrotoxicity”, “hepatotoxicity”, “neurotoxicity”, “reproductive toxicity”, “oxidative stress”, “genotoxicity” and “natural products” in titles and abstracts.

3. Properties of monosodium glutamate

The monosodium glutamate has tongue sensitivity of five flavors salt, sweet, bitter, sour, and " umami” in the taste of the Japanese language. There is no analogous word to describe taste quality in the English language. “Umami” is used by the Japanese to describe the taste of MSG as well as the meaty taste of certain fish and broth. The umami taste can be divided in two main groups: one is the a-amino acid group, represented by monosodium glutamate and the other is the 5'-nucleotide group, represented by inosine 5'-monophosphate (IMP) and guanosine monophosphate (GMP) and their derivatives [7]. Food palatability increases with appropriate concentrations of MSG. The basic sensory function of MSG is attributed to its ability to enhance the presence of other taste-active compounds. Foods containing MSG have a typical salty taste, because it contains 12.3 % sodium (e.g., one third of table salt). which interestingly is higher than for bitterness or sourness, and lower than for sweetness and equal to that for saltiness. In general, the usage level of MSG in savory foods is approximately one tenth that of salt; On the addition of MSG appropriately to sodium chloride could be reduced by 30-40 % while maintaining the same perception of saltiness. Results in taste panel studies on processed foods indicate that MSG level of 0.2-0.8 % in food by weight optimally enhances the natural food flavor [8]. Healthy food is essential for maintaining a good quality of life, especially in an aging population. MSG can improve food palatability and acceptance, increase salivary flow, and reduce oral complaints in both sick and healthy elderly. Flavors increase the number of molecules that interact with the receptors and compensate for chemosensory losses. MSG takes an additional taste but does not enhance any other tastes [9]. Bellisle et al. (1996) suggest that addition of MSG (optimal dose) to nutritionally foods would represent that everyone could use in order to selectively preference for this food or to enhance its intake of other foods (that is without increasing total energy intake). Individuals as well as the food industry [10].

4. Chemistry of MSG

MSG (Figure 2) was first extracted from the seaweed Laminaria japonica and identified by the Japanese chemist Kikunae Ikeda in 1908. It is a sodium salt of a nonessential amino acid known as L-glutamic acid with chemical formula of $C_5H_8NO_4$. Na, IUPAC-ID name of sodium 2-aminopentanedioate that specified by name of E621 in food industry (Hernandez et al., 2019). It is a white, odorless, and crystalline powder with a molecular mass of 169.11 g/mol and melting point of 232 ° C. It has a unique taste known as umami which is a savory, broth-like or meaty taste and once dissolves in aqueous solution; it will dissociate to form sodium and free glutamate. It is sparingly soluble in alcohol but the solubility in water is 385,000 mg/l at 25 ° C.

MSG is also soluble in oil or organic solvents [11]. It is a common glutamic acid salt which contains 78% glutamic acid, 22% sodium salt and also water. The major reason of using such an additive is that MSG has higher and more rapid dissolution performance against glutamic acid [12].

5. Absorption, Distribution and Excretion

Monosodium glutamate absorbed from the gut by an active transport system of amino acids. This process is suitable can be competitively inhibited; it is depended on sodium ion concentration. During the intestinal absorption, a large amount of Glutamic acid is transaminase and consequently alanine levels in portal blood are elevated. If the large amounts of glutamate are ingested, portal glutamate levels increase [13]. This elevation results increases hepatic metabolism of glutamate, leading to release of glucose, lactate, glutamine, and other amino acids into systemic circulation. The pharmacokinetics of glutamate depended on the free or incorporated into protein, and in the presence of other food components. Digestion of protein in intestinal lumen and at the brush border produces a mixture of small peptides, amino acids; di, tri-peptides such as enter the absorptive cells then intracellular hydrolysis may occur, liberating further amino acids. Defects are known in both amino acid and peptide transport Glutamic acid in dietary protein [14]. Endogenous protein secreted into the gut and digested to free amino acids and small peptides, there are absorbed into mucosal cells then peptides are hydrolyzed to free amino acids and some of the glutamate is metabolized. and Excess glutamate or other amino acids appear in portal blood. and rapid metabolism of glutamate in intestinal mucosal cells and liver. Systemic plasma levels are low, even after ingestion of large amounts of dietary protein [15].

6. Function of MSG

6.1 Central Nervous System

Glutamate is the excitatory neurotransmitter in mammalian central nervous system (CNS) playing an important role for both physiological and pathological processes (Mattson 2008). Glutamate receptors include there are three families of ionotropic receptors (NMDA – N-methyl-D-aspartate, AMPA – α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate) and three groups of metabotropic receptors (mGluR) (Meldrum 2000). They are dispersed throughout the central nervous system including amygdala, hippocampus and hypothalamus and they regulate many vital metabolic and autonomic functions. MSG is used in high doses causing neuronal necrosis in hypothalamic arcuate nuclei in neonatal rats [16].

6.2 Obesity and Metabolic Disturbance

MSG provides obesity with impaired glucose tolerance and insulin resistance. it is also effect on the energy balance disrupting the hypothalamic signaling cascade of leptin action. MSG increased mRNA expression of interleukin-6, tumor necrosis factor-alpha, resistin and leptin in visceral adipose tissue and it is also increased insulin, resistin and leptin levels or also impaired glucose tolerance [17]. MSG could induce liver injury likely as a consequence of incipient nonalcoholic steatohepatitis, contributing to inflammation. MSG increased the expression of

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several genes implicated in adipocytes differentiation, elevated serum free fatty acids, triglycerides, insulin and bile synthesis [18].

6.3 Reproductive Organs

MSG effect on reproductive system, it has been toxic effect on testis, causing oligozoospermia and increase abnormal sperm in male wistar rats. It has also caused of male infertility, testicular lesion, and alteration of sperm cell population decreases weight of pituitary glands and testes and lowered level of testosterone in male. MSG induced in female structural changes, including degenerate follicles, oocytes and medulla, congested blood vessels in the ovaries and female infertility [19].

6.4 Urolithiasis and interstitial fibrosis

MSG has been reported in adult rats alkaline urine and decreased levels of stone inhibitors such as magnesium and citrate in the urine, MSG-caused urine alkalization is still unknown but this effect was first reported by de Groot et al. (1988) [20]. MSG-administered animals may be generated higher catabolic products of glutamate in kidney cells and carbon skeleton is converted into carbon dioxide and then to bicarbonate anions and generated bicarbonates. Its absorbed back into the blood circulation and ultimately excretion of kidney extra-alkali, resulting in alkaline urine. Alkaline urine can affect the kidneys such as secreting or reabsorbing metabolites that contribute to stone formation [21].

6.5 Heptotoxicity

Liver is the largest gland in the mammalian body. The hepatocytes have metabolic functions that deal with very essential processes such as detoxification, deamination, transamination, removal of ammonia in the form of urea, biosynthesis and release of the non-essential amino acids and plasma proteins with the exception of immunogamma globulins, gluconeogenesis, storage of glycogen, conversion of carbohydrates and proteins into lipids, synthesis of lipoproteins, phospholipids and cholesterol, oxidation of fatty acids, storage of iron in the form of ferritin as well as storage of vitamins A, D and B12 [22].

6.6 Effect on immune system

Continuous intake high amounts of MSG, can increases the oxidative stress results in cytotoxicity in many organs, such as thymus. Numerous findings indicated a significant expression of glutamate receptors on immune cells. The possible relationship between glutamate concentrations and lymphocyte, inhibitory effect on lymphocyte proliferation. The latter effect is probably mediated by mGluR5 activation. It is also increasing the intracellular calcium level and via several reactions, and programmed cell death [23]. Recent findings that MSG inhibits the in vivo and in vitro proliferation of thymocytes while the inhibition depends on dose and time. this study result showed that the inhibits thymocyte proliferation was due to a decrease in cell viability, thymocytes die via apoptotic mechanism under both in vitro and in vivo conditions. MSG plays a possible role in immune disorders as well as various chronic diseases [24]. One of the mechanisms involved thymocyte apoptosis such as down-regulation of Bcl2 protein expression, MSG-induced apoptosis and altered level of Bcl-2protein in thymocytes are also related with oxidative stress. The treatment of MSG an increase in oxidative stress within the kidneys, liver, brain and thymus and presented the possible mechanism of cell toxicity. The excessive generation of oxygen reactive species (ROS) in cells damage DNA, lipids and proteins. Lipid peroxidation in cellular membranes damages the polyunsaturated fatty acids especially in lymphoid cells, and sensitizes T cells to apoptosis by decreasing the expression of Bcl-2 protein. Pro-opiomelanocortin (POMC) is a hormone precursor produce mainly in the hypothalamus and pituitary gland. In the pituitary, post-translational processing of POMC generates secretory peptide hormones adrenocorticotrophic hormone [25]. This is result showed that MSG has effects on POMC gene expression in pituitary gland and pituitary tumor cells. and also, MSG has a neuronal excitatory effect on pituitary functions that enhances POMC gene expression by increasing the stress in central nervous system in response to high doses of MSG treatment [26].

6.7 Pharmacological toxicity study

The harmful effects of MSG described in this paper might be perceived only by a small number of scientists, but they represent a silent threat posed by the consumption of this popular additive to all of society. It has been suggested that toxicity of MSG can be overcome by the use of certain kinds of vitamin like A, C, D and E. Quercetin and diltiazem have also been suggested to play a protective role in MSG-induced toxicity. Nowadays, the life-line of urban population has been formed by commercial foods due to industrialization, urbanization, and rapid increase in working class. Commercial foods are time and energy saving foods but it compromising the nutritional value of foods. The term adulteration refers to the deliberate addition of compound which is usually not present in food. These compounds are known as food additives or food adulterant. Monosodium Glutamate (MSG) is one of the most common food additives. Several studies revealed that MSG has toxic effect on fetal development/fetus, children's, adolescent, and adults. Physiological complication associated with MSG toxicity are hypertension, obesity, gastrointestinal tract troubles, and impairment of function of brain, nervous system, reproductive, and endocrine system. The effect of MSG depends upon its dose, route of administration and exposure time. Public awareness may play a major role in controlling the food adulteration by working in collaboration with National testing facilities to scrutinize each commercial food article from time to time. The aim of this review article is to highlight the deleterious impact of MSG on human health. (Table 1). Figure 2 describes the toxicity linked to MSG.

Table 1. Toxicity studies associated with MSG

Types of toxicity	**Description of toxicity reports**	**Ref**
Hepatotoxicity	In a study Monosodium glutamate (MSG) was administered to rats at doses of 0.6 and 1.6 mg/g body weight for 14 days. The results showed that body weight causes an adverse effect on the hepatic and renal function. In another study it was found that MSG in low concentration administered orally to male albino rats at doses of 5	[27]

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	mg/kg of body weight for 28 days induced hepatotoxicity. On 10 days administration to rats (by gavage) at a dose of 0.6 mg/g body weight, its result showed that MSG induced oxidative stress and hepatotoxicity. Administration MSG to adult male rats at different doses of 0.04mg /kg and 0.08mg/kg body weight for 42 days. The result has been shown that the MSG plays a critical role in the development of hepatic disorder.	
Nephrotoxicity	In the study, MSG was administered orally to adult Swiss Wistar rats at the different doses 160.7g/kg and 238.6g/kg for 28 days. The result has been shown that MSG induced hepatotoxicity and Nephrotoxicity. In the study of MSG administered to albino rats at doses 7.5mg/kg and 15 mg/kg body weight for 12 weeks. The result has been shown that the MSG induced Nephrotoxicity. In the study of MSG administered to female rats at the dose 4 mg/kg body weight for 180 days. The result has been shown that the MSG induced renal toxicity.	[28]
Neurotoxicity	Administration of MSG intraperitoneal injection to swiss Wistar male rats at the dose 2g/kg body weight for 7 days. Result has been shown that the MSG induced neurotoxicity. In another study of MSG administered to rats at the doses of 15000 mg/kg and 18000 mg/kg for 30 days. It has been observed that MSG causes neurotoxicity of the brain. In the study of MSG administered to pregnant rats at the dose 3 mg/g body weight for 30 days, it can be observed that the MSG caused acute neuronal necrosis.	[29]
Urinary-tract obstruction	On the study of MSG to administered to rats at the dose 2 mg/kg body weight for 9 month it can observed that the MSG caused alkaline urine and may increases the risks of kidney stones	[30]
Testicular Lesions	In the study of MSG administered to rats at the different doses 30 mg and 60 mg/kg body weight for 60 days. The result has been shown MSG may have some deleterious effect on the testes. Another study of MSG administered orally to rats at the different doses 1 mg/kg, 2mg/kg and 4 mg/kg body mass for 42 days. The result has been shown that MSG may have direct toxic effect on the testes. On the study of MSG administered to male wistar rats at the different doses, 6 mg/kg,17.5mg/kg 60 mg/kg body weight. For 42 days .it has been shown that the MSG induced testicular toxicity. On the	[31]

	study of MSG administered (intraperitoneal injection) to male wistar rats at the dose 4 ml/Kg body weight for 14 days. The result has been showed that the MSG have some deleterious effect in testes.	
Female infertility	On the study of MSG administered to female Sprague-Dawley rats at the different doses 0.10mg/kg,0.15mg/kg, and 0.20mg/kg body weight for14days.it has been showed that the MSG may be causes structural changes in ovaries and female infertility. In another study MSG administered to adult female wistar rats at the dose 0.04mg /kg and 0.08mg/kg body weight. The result has been showed that the structural changes in ovaries and female infertility	[32]
Fetotoxicity	On the study of MSG administered to female Wistar rats during the gestational period at the different doses 0.4g/kg and 4g/kg body weight for 0 -15th day The result has been showed that the MSG induced abnormal changes in gestation such as abortion and or resorption of fetuses. In the study of MSG administered to female Wistar rats at the dose 4 mg/g body weight for 14 days. The result has been shown that the MSG may have some deleterious effect on the ovary.	[33]
Spleen toxicity	The study of MSG administered to adult male wistar rats at the different doses of 40 mg/kg, 80 mg/kg, 120 mg/kg and 160 mg/kg body weight for 28 days. It has been shown to have an adverse effect on the spleen.	[34]
Thyroid follicular cell	On the treatment of MSG administered to male rats at the different doses of 0.25 g/kg, 3g/kg, and 6 g/kg body weight for 30 days. The result has been showed that the MSG at low doses capable to producing alterations in the body weight and thyroid tissue function	[35]
Effect of blood cell	The study of MSG administered to rats at the different doses 13.28 g/kg (88%), 6.64 g/kg (0.44%), 4.40 g/kg (0.29%) for 14 days. The result has been showed that the MSG increases number of platelets, bleeding time and clotting time	[36]
Sperm toxicity	The study of MSG administered to male rats at a dose of 4 mg /kg on postnatal days 2, 4, 6, 8, and 10 lasted for 120 days. The result has been shown that the MSG may be causing reduced sperm production and storage in the epididymis.	[37]
Fallopian tube	The study of MSG administered to female Wistar rats at doses of	[38]

	0.04 mg /kg and 0.8 mg/kg body weight for 14 days. The result has been shown that MSG may have some deleterious effects on the fallopian tube and female infertility**.**	
Effect on stomach	In the study of monosodium glutamate administered to the Adult Wistar Rats at the doses of 3g ,6g for 15 days the result has been shown that the MSG has some deleterious effect on the stomach.	[39]

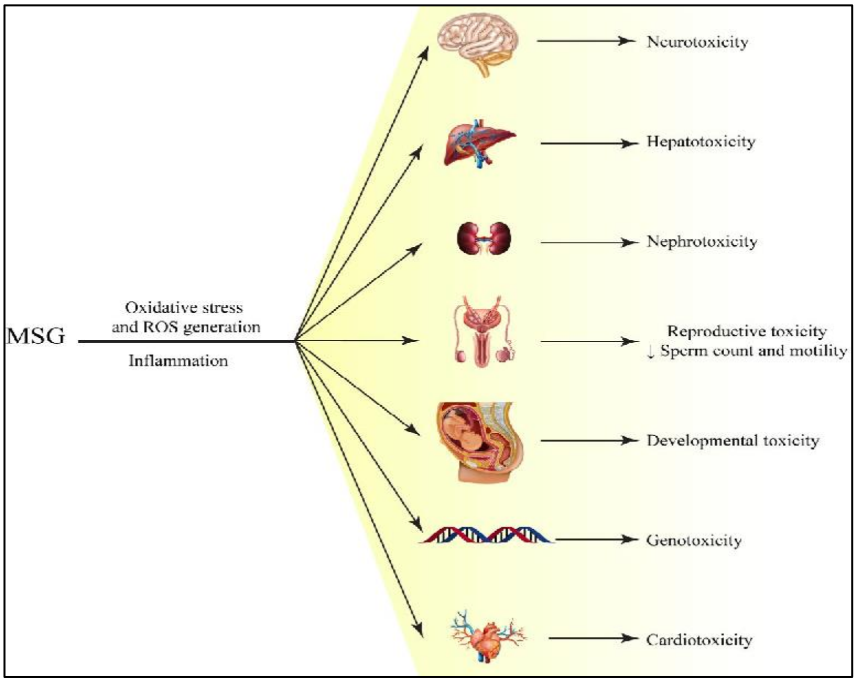

Figure 2. A schematic representation of Monosodium glutamate (MSG) toxicity and the organs may be affected by MSG

7.Protective effect of plants or plant-derived natural products

7.1 Calendula officinalis

Shivasharan et al. [40] demonstrated the protective influence of the flower extract of C. officinalis against MSG-induced oxidative stress in addition to excitotoxic brain damage in rats. Orally administered of MSG to adult Wistar rats for 7 days resulted in increasing of oxidative and nitrative stress which evidenced by the reduced GSH, GST, total thiols, catalase activity and increased the MDA and nitrite levels in the brain tissues. It was previously reported that induction of apoptosis

in the brain tissue resulted in neurotoxicity by MSG. When, animals were treated with the dosage of 100 and 200 mg/kg of the extract after one hour of MSG administration, it significantly reduced the oxidative stress through increased levels of CAT, GSH, TT, GST and reduced levels of LPO and nitrite. Since previous studies have demonstrated the antioxidant [41, 42] and inflammatory

[43, 44] activities of C. officinalis flowers, they have suggested that the observed protective activity may relate to the antioxidant and anti-inflammatory activities of C. officinalis.

7.2 Cucurbita fancifully

Numerous experimental models have demonstrated that MSG in high doses can cause the increased body weight and fat mass [45]. The increased body weight by MSG may be due to an increase in energy intake that subsequently led to obesity, or interference with signaling systems regulating appetite centers, also upscaling food consumption led to weight gain. It is accepted that increased weight is associated with several diseases such as type 2 diabetes (T2D), reduced life expectancy, cardiovascular disease, psychological dysfunction and hypertension. Recently natural medicine or plant extracts with lowering body weight activity has attracted much attention due to its fewer side effects than chemical pharmaceuticals. Previous studies in T2D patients have confirmed that *C. ficifolia* (cucurbitaceae) has hypoglycemic activity [46].

7.3 Curcuma longa

It was well-documented that *C. longa*, especially its bioactive component curcumin has numerous health effects including neuroprotective and anticancer properties. Khalil and Khedr showed that curcumin has a protective role against MSG-induced neurotoxicity in rats. Curcumin treatment considerably attenuated both AChE activity and TNFα in MSG-treated rats. They suggested that anti-inflammatory activities of curcumin may explain this neuroprotective action. In another study, Vucic and colleagues reported that treatment of rat thymocytes with curcumin decreased MSG-induced apoptosis and ROS production, restored MMP and upregulated the Bcl-2/Bax protein ratio [47]. In addition, they proposed that inhibition of PI3K/Akt signaling pathway in MSG-induced apoptosis was the main mechanism of anti-apoptotic effects of curcumin. Finally, the protective effects of curcumin on MSG induced reproductive toxicity were shown by restoring testis weight and sperm count and decreasing the incidence of abnormal sperm in male rats [48].

7.4 Hibiscus sabdariffa

Hibiscus sabdariffa belongs to the Malvaceae family, rich in several bioactive compounds such as flavonoids, anthocyanins, proanthocyanidins, polysaccharides and organic acids [49]. Olaleye *et al.* identified also a verity of other compounds such as cardiac glycosides, saponins, alkaloids, and flavonoids in aqueous extract of *H. sabdariffa.* It traditionally used to treat many diseases including liver disease, colds, hypertension, urinary tract infections, cholesterol-lowering and mutagenicity. In study of Gheller *et al.* aqueous extract of *H. sabdariffa* (at dose of 400 mg/kg/ day) exhibited considerable anti-mutagenic effects against MSG-induced DNA damage in male Wistar rats (108). The methanolic flower extract of another *Hibiscus* species*; H. tiliaceus* also has reported to have anti-mutagenic effects *in vivo*. Observed protection against mutagenic processes may be due to the presence of anthocyanins in the plants which act as potent antioxidants [50].

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7.5 Green tea

Obesity is known as an important risk factor for chronic morbidities such as cardiovascular diseases, some cancers (e.g., breast, colon and prostate), pulmonary and metabolic diseases [51]. Both experimental and clinical studies have reported the anti-obesity effects of green tea. MSG induced obesity is widely used as an experimental model for investigation of obesity and its complications. Toxic effects of MSG on neurons of hypothalamus areas that control body mass and energy metabolism was reported as major mechanism of MSG-induced obesity [52]. Study of Bártíková *et al.* showed significant anti-obesity effects of green tea. Oral administration of green tea extract (GTE) to obese mice resulted in reduction of food intake as well as level of insulin and leptin but did not significantly change the body weight [53].

7.6 Mangifera indica L (Mango)

Anthony and his colleague confirmed that MSG induced oxidative stress in brain of rats which evidenced by hypothalamic neuronal necrosis and degeneration of the brain histology. Therefore, they have studied the protective effect of mango (*Mangifera indica* L.) seed kernel against MSG toxicity in rats. Their study showed the DPPH, total antioxidant capacity (TAC), and ferric reducing antioxidant power (FRAP) *in vitro*, besides increased catalase (CAT) and superoxide dismutase (SOD) activity and reduced MDA, glutathione peroxidase (GPx), glutathione (GSH) and uric acid (UA) *in vivo*) has a significant role in improving and regulating of the brain histology and serum antioxidant capacity of normal and MSG-intoxicated rats [54]. The same author has already recorded similar results that demonstrated the modulation of MSG-induced toxicity in rats by mango seed kernel extract. Egbuonu and his coleagues have suggested that mentioned protective effect of the extract could be associated with the high vitamin C content of mango seed kernel which may enhance its antioxidant activity [55, 56]. Figure 3 describes the molecular mechanism interlinked with cell death.

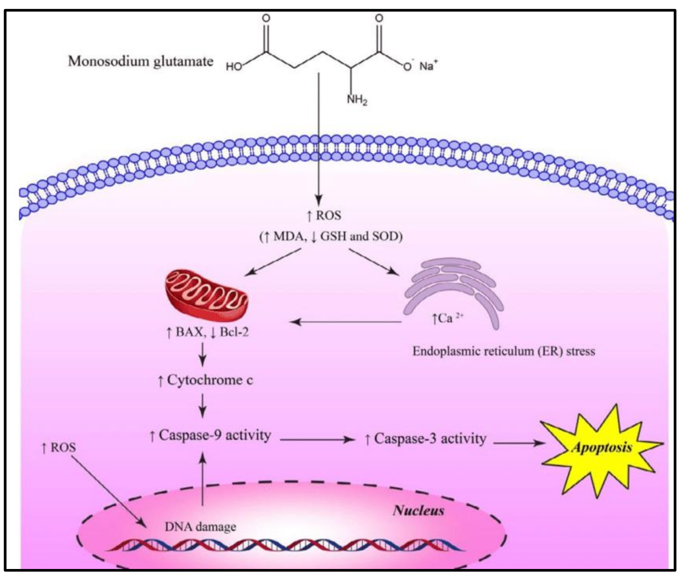

Figure 3. Molecular mechanism of monosodium glutamate (MSG)-induced cell death. As shown in the picture, MSG can activate intrinsic apoptosis pathway, leading cell death

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Conclusion

MSG as a flavor enhancer is still being widely used in a variety of food preparations. Although this substance it is generally recognized as safe for limited use by FDA, numerous studies have recently indicated unwanted side effects of long-term consumption of MSG, making its safety and toxicity a controversial issue. However, a number of *in vitro* and *in vivo* animal models and even clinical trials have shown several potential health hazards of MSG particularly at high doses. There has been a consensus by many researchers that unusual effect of MSG extends to other tissues in the body. As discussed above, MSG can increase the risk of hypercholesterolemia, hypertriglyceridemia, obesity and diabetes. Furthermore, it can induce oxidative stress, hepatotoxicity and neurotoxicity. The aforementioned undesirable effects of MSG can be minimized by some medicinal plants and their constituents. This review provides some information on the protective role of medicinal plants and their active compounds against MSG-induced toxicity.

Conflict of interest

No conflict of interest

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