Monosodium Glutamate: Review on Preclinical and Clinical Reports

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Abstract: Monosodium glutamate (MSG) is a flavor enhancer derived from L-glutamic acid, a naturally occurring amino acid in various food products. Although MSG is generally considered safe by food safety regulatory agencies, it is claimed that MSG administration may lead to neurotoxicity, cardiotoxicity, hepatic and renal disorders, and metabolic disorders. This review aimed to provide a comprehensive perspective on the potential risks of MSG administration, based on results obtained from preclinical and clinical studies regarding the alleged toxic effects of MSG. A literature search was conducted in Scopus, Google Scholar, Pubmed, and ScienceDirect databases for preclinical and clinical studies that evaluated the adverse effects of MSG administration on health. Preclinical studies showed that MSG administration was associated with obesity, cardiotoxicity, hepatotoxicity, kidney toxicity, neurotoxicity, anemia, spleen toxicity, lipid and glucose metabolism alteration, negative effects of fertility, coagulant system, and microbiota. However, clinical studies have focused mostly on MSG effects on appetite and energy expenditure. Additionally, MSG administration was associated with obesity, neurotoxicity, and increasing pain symptoms whereas did not affect the microbiota. Also, MSG can be used as a therapeutic agent in dementia patients by showing a positive effect on cognitive performance.

Keywords: monosodium glutamate; toxicity; preclinical studies; clinical studies.

1. Introduction

Monosodium glutamate (MSG), ($C_5H_8NO_4Na$), is a flavor enhancer derived from L-glutamic acid, a naturally occurring amino acid in a variety of food products [1]. Besides its flavor-enhancing properties, it is used either as a food additive (E621) in the form of hydrolyzed protein or as purified monosodium salt [2]. MSG was described as the fifth basic taste "umami" in addition to 4 flavors (sweet, sour, salty, bitter) by Kikunae Ikeda, professor of Physical Chemistry at the University of Tokyo in 1908 [1,3]. MSG was produced by extraction, a slow and costly method in this period; it was introduced in the United States of America (USA) in the late 1940s and was produced by fermentation in 1956, and in 1957, it was produced by bacterial fermentation containing genetically modified bacteria that secrete glutamic acid from their cell walls. In the 1960s, its use began widespread in the household world. It began to be added to hydrolyzed protein products such as vegetable protein, sodium caseinate, and autolyzed yeast [2]. In the last 30 years, with the development of the food industry, MSG usage

has become more popular; it has been used as a food additive in frozen entrees, crackers, canned tuna, soups, processed meats, dietary supplements, infant formula, salad dressings, some types of cheese (Roquefort, Parmesan, etc.) and vegetables (tomato, mushroom, broccoli, etc.) [1,2].

MSG has already been labeled as safe by food safety regulators. According to the US Food and Agriculture Organization (FDA) and World Health Organization (WHO) Joint Experts Committee on Food Additives (JECFA), the acceptable daily intake (ADI) level of MSG's L-glutamic acid and ammonium, calcium, monosodium, and potassium salts is set at 30 mg/kg dose in 1988 [4,5]. In 1995, the FDA included MSG in the GRAS (Generally Recognized As Safe) list in line with the report of the American Federation of Experimental Biology Associations (FASEB). According to the "Communiqué on Food Additives Excluding Colorants and Flavors" (Communiqué No: 2008/22) under the Turkish Food Codex Regulation, the usage limit of glutamic acid or its salts in all foodstuffs is 10 g/kg, and in seasoning, is QS (Unspecified amount, Quantum Sales) [6].

Although MSG is generally considered safe by food safety regulatory agencies [1], as a result of the increasing MSG usage in the food industry, it is thought that the average daily consumption in European countries is around 0.3-1.0 g/day [7], and its high-level consumption may have toxic effects [1]. These toxic effects are thought to be caused by the physiological and pathological roles that endogenous glutamate plays. There is no difference between glutamate and MSG form in terms of processes in the organism. The absorbed glutamate from the intestinal lumen is widely metabolized by enterocytes in a variety of ways, including energy production. Glutamate is the most important energy source for intestinal tissue, plays a role in intestinal protein metabolism, and is a precursor to a variety of important molecules produced in the intestinal mucosa (2-oxoglutarate, L-alanine, ornithine, arginine, proline, glutathione, γ-aminobutyric [GABA]) [8], but in high amounts uptake is mainly used in the production of ATP or conversion of other amino acids. The main products of glutamate metabolism are ornithine, glutamine, and aspartate, except for carbon dioxide production. Glutamate oxidation affects leucine oxidation due to the same reaction affinity [9]. Additionally, there is a strong relationship between an increase in glutamate concentration in the central nervous system and brain damage similar to status epilepticus, cerebral ischemia, or traumatic injuries, as well as with chronic neurodegeneration analogous to Huntington's chorea [1]. As can be seen, consumption of high doses of MSG may cause neurotoxicity, cardiotoxicity, hepatic and renal disorders, as well as metabolic disorders [1,8-10].

Especially since the 20th century, as a result of significant changes in people's diets and their tendency to specially processed foods, the consumption of food additives added to almost all processed foods and MSG consumption, which is one of them, has increased, and therefore it is critical to identify potential risks and raise public awareness [5,11,12]. This review aimed to provide a comprehensive perspective on the potential risks of MSG administration, based on results obtained from preclinical and clinical studies conducted over the past 11 years regarding the alleged toxic effects of MSG.

2. Materials and Methods

A comprehensive literature review was conducted in SCOPUS, Google Scholar, Pubmed, and ScienceDirect databases for preclinical and clinical studies that the adverse effects of MSG administration on health and published electronically. Studies evaluating the effects of MSG exposure on health increased after 2010. As a result of the search made in the relevant databases, the average number of studies increased 3-4 times in 2010 and after

compared to the years before. Therefore, we searched the literature between 2010 and 2021. Keywords used for preclinical studies were: "preclinical studies", "*in vivo*" and "monosodium glutamate", "flavor enhancer", "umami substance", "umami molecule" and "toxicity", "effects", "health", "obesity", "insulin resistance", "oxidative stress", "lipid metabolism", "cardiovascular toxicity", "heart toxicity", "liver toxicity", "kidney toxicity", "neurotoxicity", "testicular toxicity", "ovary toxicity", "microbiota" and "metabolomics". Accordingly, a total of 35 articles were included in this review. Keywords used for clinical studies were: "clinical studies" and "monosodium glutamate," "flavor enhancer," "umami substance," "umami molecule," and "toxicity," "health", "effects", "obesity", "appetite", "pain", "insulin resistance", "lipid metabolism", "neurotoxicity" and "microbiota". In line with these criteria, 19 clinical studies were included in the review, 2 of which were *in vitro* studies performed on human nerve cells.

The inclusion criteria were: (1) preclinical and clinical studies about MSG consumption and health effects, (2) the paper is written in English, (3) in order to interpret the results of preclinical and clinical studies if there are no human studies, studies which evaluated the effect of MSG exposure in human cells. The exclusion criteria were: (1) *in vitro* studies about MSG exposure, (2) the papers are written in other languages, (3) thesis, letters to the editor, and conference abstracts.

3. Results and Discussion

Before presenting and discussing the results of the literature review, we present a figure of MSG administration and its health effects (Figure 1).

3.1. Preclinical studies on MSG exposure.

We included preclinical studies which determined different administration doses of MSG orally, intraperitoneally, or subcutaneously in order to examine its effects on biochemical parameters and the histology and morphology of the liver, heart, kidney, ovaries, testicles, spleen, as well as nervous system, metabolomics, and microbiota. The results showed that MSG administration was related to many abnormalities in metabolism: glucose and lipid metabolism, oxidative stress, cardiovascular and coagulant system, liver, kidney, spleen and fertility, neuronal losses, and the microbiota (Table 1).

3.1.1. Effects on obesity.

Obesity is a metabolic disorder with an increasing worldwide prevalence. It has long been recognized as an independent risk factor for a variety of chronic diseases such as type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension (HT), stroke, and cardiovascular diseases (CVD) [13]. Although studies evaluating the effects of MSG on obesity are contradictory, they agree that it affects the general negatively (Table 1).

Orally administration of MSG (4 mg/g *bw*/daily for 2 to 4 weeks) was associated with increased body weight in rats. Also, the thickness of the zona fasciculata (ZF) increased in the group who consumed MSG for 2 weeks, whereas the thickness of the ZF decreased in the group who consumed MSG for 4 weeks, and this result was not statistically significant. The study showed that these changes were reversible, but it might take long to return to normal levels [13]. The doses of 100 mg, 400 mg, 2 or 4 g /kg *bw*/daily of MSG for 60 days led to an increase in body weight in rats regardless of dose [14]. Similarly, MSG supplementation (500, 750,

1000, or 1250 mg/kg *bw*/daily for 8 weeks) was observed to raise body weight gain. Bodyweight gain was higher in the group consuming the dose of 750 mg/kg *bw*/daily compared to the others [15]. Another study evaluated the effect of commercial or analar MSG supplementation and found that the supplementation doses of 0.1, 0.15, or 0.2 g/kg *bw*/twice daily of analar-grade MSG and the dose of 0.2 g/kg *bw*/twice daily commercial food-grade MSG for 14 days increased appetite, thirst, and body weight gain [16]. Obesity, hyperphagia, and steatosis occurred in mice as a result of MSG supplementation of 2 g/kg *bw*/daily for 5 days with or without dietary restriction [17].

Moreover, studies are showing that MSG supplementation has no effect on body weight in the literature. For example, it was reported that orally administrated MSG (4 g/kg *bw*/daily for 10 days) did not increase body weight gain in male rats [18]. Another study showed that 2 mg/g *bw*/daily of MSG supplementation for different durations (1, 3, 6, and 9 months for 2 weeks) did not affect body weight [19]. The doses of 30 or 60 mg/kg *bw i.p.* of MSG supplementation did not change body weight significantly after 28 days in mice [20]. Also, a recent study found that 48.7 g to 94.6 g of MSG for 8 weeks had no adverse effect on body weight in rats [21].

Thus, many preclinical studies showed that MSG was associated with body weight gain, whereas some of them did not. However, the duration times and the routes of administration used is important to indicate a threat to human health. Subcutaneous or intraperitoneal administrations of doses several folds higher than human dietary intake have little relevance for human MSG exposure since these routes overcome the normal metabolic pathway of ingested glutamate.

3.1.2. Effects on lipid and glucose metabolism.

Insulin is involved in lipid metabolism as well as carbohydrate metabolism, and insulin insufficiency is also associated with hypercholesterolemia and hypertriglyceridemia, as in DM. Additionally, hypercholesterolemia is one of the leading risk factors of CVD [22].

A study found that the dose of 4 g/kg *bw*/daily of MSG supplementation subcutaneously on days 2, 4, 6, 8, 10, 12 significantly increased total cholesterol (TC), triglyceride (TG), and malondialdehyde (MDA) levels in serum, whereas decreased high-density lipoprotein (HDL) in serum and glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) levels in heart tissue in newborn rats [23]. Similarly, the administration of MSG (4g/kg *bw*/daily after birth for 5 days) increased TC and insulin levels, leading to metabolic syndrome (MetS)-like features in mice [24].

In adult rats, analar grade MSG supplementation with 0.10, 0.15, or 0.20 g/kg *bw*/twice daily or commercial grade MSG supplementation with 0.20 g/kg *bw*/twice daily for 14 days increased serum glucose levels; however, total protein, TC, and bilirubin levels increased in only analar grade MSG groups [16]. The addition of 4g/kg *bw*/daily MSG for 10 days showed a significant increase in glucose-6-phosphatase activity, whereas a significant decrease in glucose-6-phosphate dehydrogenase activity and higher blood glucose levels in rats [18]. In another study, it was found that as a result of MSG supplementation (500, 750, 1000, or 1250 mg/kg *bw*/daily for 8 weeks), TC decreased in all MSG groups, and fasting blood glucose increased in all MSG groups (except 500 mg/kg *bw*/daily) despite a slight decrease in the group of the dose of 500 mg/kg *bw*/daily. For this reason, the study showed that the increase in blood glucose by MSG is an indication that it can induce DM [22].

Moreover, a study indicated that the dose of 2 mg/g *bw*/daily of MSG supplementation at different duration (1, 3, 6, and 9 months) for 2 weeks, MSG-supplemented rats had significantly lower pancreatic β-cell mass at 1, 6, and 9 months, also, MSG supplementation was not affected serum insulin levels and glucose tolerance compared to the control group [19].

According to the results of studies, MSG exposure was negatively affected glucose and lipid metabolism so that these changes could cause many metabolic dysfunctions, but the dietary intake of humans has poor relevance for human exposure to MSG.

3.1.3. Evaluation of cardiovascular toxicity.

Cardiovascular diseases are complex and many metabolic disorders, especially oxidative stress, play a role in their development [25]. Two preclinical studies have been found in the literature showing the adverse effects of MSG supplementation on the cardiovascular system. In healthy rats, a single dose of 0.5 g /kg *bw* intravenous *(i.v.)* of MSG supplementation caused a decrease in heart rate, while 1.5 g/kg *bw i.v.* of MSG supplementation caused bradycardia. In addition, the dose of 1.5 g/kg *bw*/daily of MSG induced ventricular tachyarrhythmia in rats with acute myocardial infarction [26]. In another study, rats were divided into 3 groups: control, 4 mg/kg *bw*/daily of MSG for 42 days, 8 mg/kg *bw*/daily of MSG for 42 days. The enlargement of the Bowman's space, mild shrinkage of the glomerulus, hemorrhages, and tubular dilatation were observed by the MSG supplementation, and the severity increased with dosage. There was an increase in the size and number of fibroblasts compared to the control group [27].

In conclusion, these studies are limited to indicating a comprehensive result. Also, these experimental conditions do not mimic human dietary consumption of MSG and have poorly related to humans.

3.1.4. Evaluation of liver toxicity.

MSG can damage the pathway from the arcuate nucleus of the hypothalamus to the paraventricular nuclei, causing obesity, fatty liver, inflammatory cell infiltration, and fibrosis [20]. Additionally, many preclinical studies show that MSG supplementation negatively affects the morphological structure of the liver and its enzymes (Table 1).

A single dose of 4 g/kg *bw*/daily of MSG supplementation on days 2, 4, 6, 8, 10, 12, and 14 to newborn rats increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels [23]. After 5 days, the same dose of MSG caused microvesicular steatosis and inflammatory cell infiltration in the liver, as well as enlarged adipocytes and crown-like structures in the epididymal fat; and increased frequencies of monocytes and M-1 macrophages in the liver and epididymal adipose tissue in newborn mice [24].

Administered 6 mg/g *bw*/daily of MSG for 45 days induced central vessel dilatation, severe cytoarchitectural distortions of hepatocytes, vacuumed cytoplasm, swollen mitochondria and pycnotic core vesicles, impaired endoplasmic reticulum, and marked decrease in mucopolysaccharide content with the accumulation of collagen in hepatocytes and degradation connective tissue; and significant expression of ki-67 and p53 pro-apoptotic proteins in rats' hepatocytes [28]. The doses of 0.10, 0.15, or 0.20 g/kg *bw* analar grade MSG supplementation or the dose of 0.20 g/kg *bw* commercial-grade MSG supplementation twice daily for 14 days increased AST and ALT levels in rats [16]. Similarly, 5 g/kg *bw*/daily of MSG for 30 days increased AST, ALT, and alkaline phosphatase (ALP) levels in rats [29]. A

recent study also found that 2, 4, or 8 g/kg *bw* of MSG for 14 days increased hepatic enzyme activities (ALT, AST, ALP) and distorted cytoarchitectural integrity of the liver [30]. In another study, after 8 weeks of administration of 500, 750, 1000, or 1250 mg/kg *bw/*daily MSG increased ALT levels, especially in those consuming 500 mg/kg *bw/*daily [15]. The dose of 4 mg/kg *bw/*daily of MSG supplementation after 90 days enhanced ALT, AST TC, TG, and MDA, and decreased SOD and GSH levels in rats. Additionally, steatosis occurred in these rats: increased vacuolation, extensive fibrosis, and apoptosis in the hepatic cells, especially centrilobular. MSG cessation partially improved biochemical and pathological changes but did not return it to normal [31]. A recent study observed that 2 g/kg *bw* of MSG for 4 weeks caused severe damage in the hepatic tissues such as congestion and dilatation of blood vessels with different cellular changes, including; necrosis, apoptosis, polymorphism, and prominent Kupffer cells [32]. According to a study, MSG supplementation of 1 g/5 mL/kg *bw* from day 0 to day 20 of gestation resulted in a reduction of SOD, GSH activities in addition to the elevated TNF-α and NO in liver tissue of pregnant mothers and their fetuses [33].

Moreover, it was reported that subcutaneously administered MSG (2 g/kg *bw/*daily) determined an increasing body weight, visceral fat, TC, TG, LDL, and ALT levels in mice with and without dietary restrictions and led to major liver steatosis in addition, MSG- unrestricted diet group showed lower TC and LDL levels compared to MSG-restricted diet group after 6 months. While the adverse effects caused by MSG were reversible in the 12th month for the MSG-restricted diet group, steatohepatitis, mild fibrosis, and liver nodules occurred at the end of the 12th month in the MSG-unrestricted diet group [17].

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 of gestation. The pregnant mothers were then divided into two sub-groups; the first was dissected on the 15th day of gestation, and the second was on the 19th. MSG supplementation caused vacuolation in hepatocytes, degenerative and necrotic areas, and atrophied size of hepatocytes with pyknotic nuclei in both maternal and fetal liver tissues. The centrilobular and portal zones showed these alterations [34].

The nine studies included in this review showing alterations in hepatic morphology, liver enzymes, and antioxidant defense were observed for different doses, times, and routes of MSG administration. However, these studies fall short of mimicking the metabolic pathways in humans.

3.1.5. Evaluation of kidney toxicity.

MSG supplementation can cause oxidative stress through depletion of endogenous antioxidants in the kidneys by increasing reactive oxygen species (ROS), which leads to oxidation of lipids, proteins, DNA, RNA, and cellular damage [18,35].

It was exhibited that the dose of 4 g/kg *bw/*daily MSG supplementation for 10 days increased lipid peroxidation and decreased GSH, SOD, and CAT levels in the kidney. It also resulted in a decrease in the activity of glucose-6-phosphate dehydrogenase and significantly higher blood glucose and renal glucose concentration [18]. In another study, MSG supplementation (4 g/kg *bw/*daily for 180 days) significantly increased kidney function parameters (urea, uric acid, and creatinine), lipid peroxidation markers (MDA and conjugated dienes), and altered antioxidant system (SOD, CAT, glutathione peroxidase, glutathione transferase, and reduced glutathione). Congested glomeruli, tubular swelling, capillary congestion, and microhemorrhages in the tubular stroma were all observed in the kidney [35].

Additionally, 3 g/kg *bw* of MSG for 6 months dramatically increased the serum levels of MDA, BUN, creatinine, uric acid and renal Caspase-9, NGAL, and KIM-1 expression in rats [36].

The dose of 2 mg/g *bw*/daily of MSG in drinking water for 9 months caused alkalized urine and more kidney stone formation predisposition with increased activity of calcium phosphate. Moreover, hydronephrosis occurred in 20% of the rats, while MSG supplementation increased serum creatinine and potassium levels, including urine output volume, urinary sodium, and citrate excretion; reduced ammonium and magnesium excretion [37]. 5 g/kg *bw*/daily MSG supplementation for 30 days increased serum urea and creatinine levels and negatively affected renal functions in rats [29]. Similarly, a recent study found that different doses of MSG (500 mg/kg, 750 mg/kg, 1000 mg/kg, and 1250 mg/kg *bw* for 8 weeks) increased the concentrations of creatinine, urea, total bilirubin, conjugated bilirubin and unconjugated bilirubin [38]. Additionally, 15 mg/kg *bw* of MSG for 30 and 60 days caused an enlargement in a mesangial mass characterized by hypertrophy and hyperplasia of mesangial cells, resulting in mesangial proliferative glomerulonephritis in rats [39].

These studies indicated that MSG exposure shows an adverse effect on function parameters, morphology, and histology of the kidney and alters antioxidant defense. Moreover, the studies are limited to proving human health.

3.1.6. Evaluation of neurotoxicity.

In the body, MSG dissociates into sodium and glutamate ions. Glutamate is the predominant excitatory neurotransmitter in the brain and is important in synaptic plasticity, learning, and development. The neurotoxic effects of glutamate have been associated with the overactivation of excitatory amino acid receptors, increasing intracellular calcium that triggers a cascade of enzymatic activities that lead to cell death [40].

MSG supplementation (4 mg/g *bw*/daily) to newborn rats on days 1, 3, 5, and 7; modified hippocampal expression of the NMDAR (-methyl-d-aspartate receptor) subunit NR1 and the AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor) subunits GluR1/GluR2 at postnatal days 8, 10, 12, and 14. Also, MSG altered the P38 MAPK (P38 mitogen-activated protein kinases) pathway, therefore increasing the expression of the NRSF gene silencing factor and causing the loss of neurons [41].

In adult rats, 2 g/kg *bw i.p* of MSG for 7 days induced excitotoxic neural damage and elevated levels of ROS [42]. Administration doses of 40 and 80 g/kg *bw*/daily MSG supplementation for 28 days was associated with neuronal damage in the brain, hippocampus, and cerebellum; increased glutamate and glutamine in the brain and plasma, decreased SOD and CAT; and increased nitric oxide (NO) in the brain [38]. It was observed that 4 and 6 mg/g *bw* MSG supplementation for 30 days was increased neuronal damage in the hippocampus in dose-dependent [43]. In another study, MSG supplementation at 5 g/kg *bw*/daily for 30 days resulted in an increase of levels of brain and serum MDA, lactate dehydrogenase, serum cholinesterase (ChE), total creatine phosphokinase (CPK), and creatine phosphokinase isoenzymes BB and CPK (CPK-BB). Furthermore, MSG increased glutathione s-transferase (GST), CAT, and SOD activities, decreased GSH levels, and caused an impairment in antioxidant homeostasis [44]. Similarly, the dose of 2 g/kg *bw*/daily MSG supplementation for 7 days resulted in a significant decrease in spontaneous locomotor activity, increased lipid peroxidation and NO, decreased GST and CAT activity, resulting in impaired oxidative defense in brain tissue and changes in hippocampal neuron histology in rats [45]. The same dose and time of MSG altered behavioral and physiological changes (such as aggression, muscle

weakness, and decreased locomotor activity); caused loss hippocampal loss, significant cerebral edema, neuronal eosinophilia, and decreased levels of GSH, SOD, and CAT in the brain in rats [46]. After 30 days administration of 8 mg/kg *bw*/daily MSG, 32 mg/kg *bw*/daily aspartame, or both of them decreased locomotor activity and neuromuscular coordination (grip strength): increased non-social behavior by causing numerous disorders in fear and anxiety behavior in each group; and reduced the perception of attack and biting in case of a threat in mice. Also, motor activities and neuromuscular transmission have been disturbed [47].

Rats were given 100 mg, 400 mg, 2 or 4 g/kg *bw*/daily MSG supplementation for 60 days, and one group analyzed body weight, T-maze test, novel object recognition test (NOR) and striato-hippocampal acetylcholinesterase (achE) level immediately after 60 days. The other group was kept free of MSG for further 60 days and analyzed at 120 days. It showed that the rats in the first group neither have a dose-dependent reduced T-maze response and discrimination index in the NOR test and an increase in body weight and AchE level. However, the changes were statistically significant in the group receiving 4 g/kg *bw*/daily MSG supplement. For the second group, these results did not found significantly different compared to the control group. The study found that long-term administration of MSG caused cognitive impairment, but not permanent throughout life due to normal diet and natural recovery mechanisms in the body improving the toxic effects of MSG, and only cognitive parameters ameliorated gradually after a long time [14].

Concerning MSG's effects on the nervous system and behavior, MSG exposure changed morphological structures in the cerebrum, hippocampus, and cerebellum, and the antioxidant defense in the brain. Also, MSG administration led to the loss of neurons. We consider further studies, using appropriate dosages and administration routes, are necessary to evaluate the toxicity of chronic MSG exposure on the nervous system.

3.1.7. Effects on fertility.

Important toxicity determined by preclinical studies is the adverse effects of MSG exposure on ovaries and testicles (Table 1).

In female rats, cellular hypertrophy of theca follicles, disruption of the basement membrane separating theca follicles from zona granulosa, and degenerative and atrophic changes in the oocyte were reported following MSG administration (0.04 or 0.08 mg/kg *bw*/daily for 14 days), in a dose depending manner [48]. MSG at the same time and doses caused morphological changes in the fallopian tubes (cellular hypertrophy of the columnar epithelium, disruption of the basement membrane separating the endosalpinx from the myosalpinx), with more severe changes in the group that received 0.08 mg/kg *bw* of MSG in rats [49]. MSG doses of 0.1, 0.15, or 0.2 g/kg bw/3 times per day for 2 weeks induced inflammatory cell infiltration in and around the oocyte and in the zonal granulosa layer, as well as tissue architecture deterioration [50].

Administered 4 g/kg *bw*/daily MSG for 14 days caused abnormalities in spermatogenic cells and spermatogenic cell loss in male rats. These abnormalities were: atrophy of seminiferous tubules, intercellular vacuuming in the stroma and peritubular fibrosis; decreased testicular weight, tubular diameter, and germinal epithelium height, decreased in the spermatic count [51]. The dose of 4 mg/g *bw*/daily MSG supplementation for 15 and 45 days did not significantly reduce sperm motility and concentrations compared to the control group. Still, MSG supplementation significantly reduced sperm viability and abnormality in rats. Long-term administration of MSG resulted in primary abnormality formation (round and double-

headed sperm) and increased secondary abnormalities (bent neck, curve tail, coiled tail, headless and tailless) compared to control [52]. Moreover, supplementation of paclitaxel (PTX) treatment and MSG (30 or 60 mg/kg bw for 28 days) in male mice induced more testicular tissue changes due to chemotherapy. MSG supplementation decreased the histomorphometry indices, germ cells population, and microscopic indices of spermatogenesis. In addition, MSG administration before PTX treatment caused more changes [20].

Considering all of the above, MSG negatively affects fertility and fetal development but makes it difficult to evaluate results according to human dietary intake due to differences in administration routes.

3.1.8. Other effects related to MSG exposure.

Anemia is a common disease due to various reasons. In addition, the results of the studies evaluating the effect of MSG on anemia biomarkers are contradictory. For example, red blood cell count, packed cell volume, hemoglobin (Hb) concentration, white blood cell count platelets count significantly decreased in mice receiving MSG (8 mg/kg *bw*/daily for 30 days), aspartame (32 mg/kg *bw*/daily for 30 days) or both of them [47]. In another study, the addition of 5 g/kg *bw*/daily of MSG for 30 days significantly decreased red blood cell count, Hb, mean erythrocyte hemoglobin concentration (MCHC) levels, therefore increasing the risk of anemia in rats [29]. In a study conducted on pigs, MSG supplementation (10 g/kg *bw*/daily for 30 days) increased serum iron level and iron-binding capacity [53]. According to the studies, the difference may be since the study was conducted in different rodent groups.

The hemostasis process is divided into vascular, platelet, and coagulation phases. The tests available for the first phase are bleeding time, platelet count, and platelet function analysis. However, available tests to evaluate the coagulation phase of hemostasis are whole blood clotting time, prothrombin time, active plasma thromboplastin time, and thrombin time. Bleeding time is affected by a large number of diseases, drugs, physiological factors, test conditions, and therapeutic actions. A study evaluating the effect of MSG supplementation (4.40, 6.64 ve 13.28 g/kg *bw*/daily for 14 days) on the anticoagulant system showed that the doses of 6.64 and 13.28 g/kg *bw*/daily of MSG supplementation significantly increase platelet cell counts, platelet count, bleeding time, and clotting time in rats [54].

The spleen, the largest secondary lymphoid organ, is considered the drainage site for intravenously administered compounds and is therefore considered an important organ for evaluating treatment-related lesions. Similar to the other studies' results, less atrophy was found in rats sacrificed at day 42 compared to rats sacrificed at 14 and 28 days after MSG supplementation with 4 mg/kg *bw*/daily for 14 days. The study stated that MSG supplementation might affect the spleen negatively in rats which is reversible and non-permanent damage, but it may take a long time to regain the normal structure of the spleen [55]. Further studies are needed to evaluate the effects of chronic MSG exposure on human spleen structure.

Changes in the metabolome can provide insight into the metabolic processes of cells, tissues, or the whole body. In one study, newborn pigs on the same day with the same body weight were divided into 4 groups: 0.09 g/kg *bw*/daily NaCl (CN group), 0.03 g/kg *bw*/daily MSG (LMG group), 0.25 g/kg *bw*/daily MSG (MMG group), and 0.50 g/kg *bw*/daily MSG (HMG group) was given twice daily as a supplement. MSG supplementation after 7 days significantly reduced serum citrate content, significantly increased serum trimethylamine content, and decreased unsaturated fat content, especially in HMG group.

Table 1. Summary of preclinical studies associating MSG exposure.

Animal Model	Duration and dosage of MSG	Administration Route	Results
EFFECTS ON OBESITY			
Male Albino rats (n=40) [10]	4 weeks, 4 mg/g *bw*	Oral	There was an increase in body weight; 2 weeks of consumption led to an increase in the thickness of the ZF, while 4 weeks of consumption decreased the thickness of the ZF, but this was not statistically significant.
Wistar rats (n=40) [15]	8 weeks, 500, 750, 1000 or 1250 mg/kg *bw*	Mixed with diet	While an increase was observed in body weight and ALT levels in all MSG groups, the increase in body weight was higher in those who consumed 750 mg/kg, and ALT activity was higher in those who consumed 500 mg/kg.
Albino rats (n=24) [21]	8 weeks, 48.7 g to 94.6 g	Oral	There was no significant difference in the average weights.
EFFECTS ON LIPID AND GLUCOSE METABOLISM			
Newborn Wistar rats (n=10) [23]	On days 2, 4, 6, 8, 10, 12 and 14, 4 g/kg *bw*	Subcutaneously	The levels of TC, TG, MDA increased in serum while HDL level in serum and GSH, SOD, and CAT levels in the heart decreased.
Male Wistar rats (n=80) [19]	2 weeks at 1, 3, 6 and 9 months; 2 mg/g *bw*	Oral	MSG consumption did not change body weight but increased the feeling of thirst. Pancreatic cell mass was significantly reduced with supplements at 1, 6, and 9 months of age, and pancreatic cell fibrosis was higher at 1 and 3 months of supplements. Although MSG caused the pancreatic mass loss, no significant difference was observed between serum insulin levels and glucose tolerance compared to control.
Wistar rats (n=40) [22]	8 weeks, 500, 750, 1000 or 1250 mg/kg *bw*	Mixed with diet	MSG consumption decreased the TC level in all groups and increased fasting blood glucose.
EFFECTS ON CARDIOVASCULAR SYSTEM			
Male Albino rats (n=60) [28]	45 days, 6 mg/g *bw*	Mixed with diet	MSG induced central vessel dilatation, severe cytoarchitectural distortions of hepatocytes, vacuumed cytoplasm, swollen mitochondria and pycnotic core vesicles, impaired endoplasmic reticulum and marked decrease in mucopolysaccharide content with the accumulation of collagen in hepatocytes and degradation connective tissue; and significant expression of ki-67 and p53 pro-apoptotic proteins in rats' hepatocytes.
Wistar rats (n=72) [26]	Single dose, 0.5 or 1.5 g/kg *bw*	Intravenous	0.5 g/kg of MSG decreased heart rate, while 1.5 g/kg of MSG caused bradycardia. In addition, the dose of 1.5 g/kg f MSG induced ventricular tachyarrhythmia with acute myocardial infarction
Albino rats (n=30) [27]	42 days, 4 or 8 mg/kg *bw*	Oral	Depending on the dose, the enlargement of the Bowman's space, mild shrinkage of the glomerulus, hemorrhages, and tubular dilatation were observed.
EFFECTS ON KIDNEY			
Male Wistar rats (n=36) [35]	180 days, 4 g/kg *bw*	Oral	An altered antioxidant system was observed by increasing kidney function markers, lipid peroxidation markers. Additionally, congested glomeruli, tubular swelling, capillary congestion, and microhemorrhages in the tubular stroma were all observed in the kidney.
Male Wistar rats (n=24) [18]	10 days, 4g/kg *bw*	Oral	MSG did not affect body weight and protein concentration but increased lipid peroxidation and reduced GSH, SOD, and CAT levels in the kidney. There was also a significant decrease in the activity of glucose-6-phosphate dehydrogenase and significantly higher blood glucose and renal glucose concentration.
Male Wistar rats (n=20) [37]	9 months, 2 mg/g *bw*	Oral	MSG caused alkalized urine and more kidney stone formation predisposition with increased activity of calcium phosphate. Hydronephrosis occurred in 20% of the rats, and MSG increased serum creatinine and potassium levels, including urine output volume, urinary sodium, and citrate excretion, whereas reduced ammonium and magnesium excretion.

Animal Model	Duration and dosage of MSG	Administration Route	Results
Rats (n=20) [29]	30 days, 5g/kg *bw*	Mixed with diet	Red blood cell count, Hb, MCHC levels decreased, and AST, ALT, ALP, serum urea, and creatinine levels increased.
Wistar rats (n=25) [38]	8 weeks, 500 mg/kg, 750 mg/kg, 1000 mg/kg, and 1250 mg/kg *bw*	Mixed with diet	MSG increased the concentrations of creatinine, urea, total bilirubin, conjugated bilirubin, and unconjugated bilirubin.
Male rats (n=60) [36]	6 months, 3 g/kg *bw*	Oral	MSG significantly increased the serum level of MDA, BUN, creatinine, uric acid, renal Caspase-9, NGAL, and KIM-1 expression in rats.
Male rats (n=40) [39]	30 or 60 days, 15 mg/kg *bw*	Oral	Long-term intake of MSG caused indirect narrowing of the glomerular capillary lumen, causing kidney failure.
EFFECTS ON LIVER			
Newborn male mice (n=6) [24]	5 days after birth, a single dose 4 g/kg *bw*	Subcutaneously	There was an increase in serum insulin and TC levels. Also, MSG caused microvesicular steatosis and inflammatory cell infiltration in the liver, as well as enlarged adipocytes and crown-like structures in the epididymal fat; and increased frequencies of monocytes and M-1 macrophages in the liver and epididymal adipose tissue in newborn mice.
Mice (n=54) [17]	5 days, 2 g/kg *bw*	Subcutaneously	MSG led to an increase in body weight, visceral fat, TC, TG, LDL, and ALT levels with and without dietary restrictions. After 6 months, TG, LDL, and ALT levels were increased, and steatosis occurred. MSG supplementation and restricted diet were reversible after 12 months, and those without dietary restrictions had steatohepatitis, mild fibrosis, and liver nodules.
Male Sprague Dawley rats (n=36) [31]	90 days, 4 mg/kg *bw*	Oral	An increase in ALT, AST, TC, TG, and MDA levels and a decrease in SOD and GSH levels were observed. Steatosis has occurred.
Sprague Dawley rats (n=50) [16]	14 days, 0.10, 0.15 or 0.20 g/kg *bw* analar grade MSG or 0.20 g/kg *bw* commercial grade MSG twice daily	Oral	All MSG supplements increased body weight with a sense of appetite and thirst and AST and ALT levels.
Pregnant female albino rats (n=50) [34]	9th to 14th of gestation, 7 g/10mL/kg *bw*	Oral	Vacuolation in hepatocytes, degenerative and necrotic areas, and atrophied size of hepatocytes with pyknotic nuclei were observed in maternal and fetal liver tissues.
Male Albino rats (n=40) [32]	4 weeks, 2 g/kg *bw*	Oral	MSG caused severe damage in the hepatic tissues, such as congestion and dilatation of blood vessels with different cellular changes, including; necrosis, apoptosis, polymorphism, and prominent Kupffer cells. Additionally, body weight was increased by MSG supplementation.
female Albino rats (n=16) [33]	0-20 days of gestation, 1 g/5 mL/kg *bw*	Oral	MSG reduced SOD, GSH activities in addition to the elevated TNF-α and NO in liver tissue of pregnant mothers and their fetuses.
Male Swiss mice (n=24) [30]	14 days, 2, 4, or 8 g/kg *bw*	Oral	MSG increased hepatic enzyme activities (ALT, AST, ALP) and distorted the cytoarchitectural integrity of the liver.

EFFECTS ON NERVOUS SYSTEM

Animal Model	Duration and dosage of MSG	Administration Route	Results
Adult female Wistar rats (n=30) [45]	7 days, 2 g/kg *bw*	Intraperitoneal	Significant reduction in spontaneous locomotor activity increased lipid peroxide and NO levels, and decreased GSH and CAT activities were seen in brain tissue.
Albino Wistar rats (n=30) [46]	7 days, 2 g/kg *bw*	Intraperitoneal	Alteration behavioral and physiological changes (aggression, decreased locomotor activity, and muscle weakness); hippocampal loss, significant cerebral edema, neuronal eosinophilia, and a decrease in GSH, SOD, and CAT activities in brain tissue were found.
Newborn Wistar rats (n=8) [40]	On 1, 3, 5, and 7 days, 4 mg/g *bw*	Subcutaneously	By altering the expression of the hippocampal NMDAR receptor subunit NR1 of AMPAR receptor subunits GluR1 / GluR2; through the P38 MAPK pathway, NRSF increased the expression of the gene silencing factor and caused the loss of neurons.
Rats (n=36) [42]	7 days, 2 mg/kg *bw*	Intraperitoneal	Induced excitotoxic neural damage and elevated levels of ROS.
Sprague-Dawley rats (n= 25) [43]	30 days, 4 and 6 mg/g *bw*	Oral	Neuronal damage in the hippocampus increased with dose-dependent.
Mice (n=40) [38]	28 days, 10, 20, 40 or 80 mg/kg *bw*	Oral	40 and 80 mg/kg of MSG caused neuronal damage in the brain, hippocampus, and cerebellum and showed increased levels of NO, glutamate, and glutamine in the brain while decreasing SOD and CAT levels in the brain.
Male Wistar rats, (n=8) [44]	30 days, 5 mg/kg *bw*	Subcutaneously	MSG increased MDA, lactate dehydrogenase, serum ChE, CPK, CPK-BB in the brain, and serum. Also, GST, CAT and SOD activities increased, whereas GSH levels decreased.
EFFECTS ON FERTILITY			
Female Wistar rats (n=16) [48]	14 days, 0.04 or 0.08 mg/kg *bw*	Mixed with diet	Morphological changes in the ovaries (cellular hypertrophy of theca follicles, disruption of the basement membrane separating theca follicles from zona granulosa), degenerative and atrophic changes in the oocyte occurred in a dose-dependent manner.
Female Wistar rats (n=16) [49]	14 days, 0.04 or 0.08 mg/kg *bw*	Mixed with diet	Morphological changes of the fallopian tubes (cellular hypertrophy of the columnar epithelium, disruption of the basement membrane separating the endosalpinx from the myosalpinx) occurred in a dose-dependent manner.
Male Wistar rats (n=24) [51]	14 days, 4g/kg *bw*	Intraperitoneal	Abnormalities in spermatogenic cells and spermatogenic cell loss were observed. These abnormalities were: atrophy of seminiferous tubules, intercellular vacuuming in the stroma and peritubular fibrosis; decreased testicular weight, tubular diameter, and germinal epithelium height, decrease in the spermatic count.
Female Wistar rats (n=20) [50]	14 days, 0.1, 0.15 or 0.2 g/kg *bw*	Oral	Infiltration of inflammatory cells in and around the oocyte and in the zonal granulosa layer and deterioration in tissue architecture were found.
Male mice (n=48) [20]	28 days, 30 or 60 mg/kg *bw*	Intraperitoneal	PTX treatment and MSG supplementation induced more testicular tissue changes due to chemotherapy. MSG decreased the histomorphometry indices, germ cells population, and microscopic indices of spermatogenesis. Also, MSG administration before PTX treatment caused more changes.
Male Wistar rats (n= 12) [52]	15 or 45 days, 4 mg/g *bw*	Oral gavage	MSG for 15 and 45 days did not significantly reduce sperm motility and concentrations but significantly reduced sperm viability and abnormality. 45 days of MSG administration resulted in primary abnormality formation (round and double-headed sperm) and increased secondary abnormalities (bent neck, curve tail, coiled tail, headless and tailless) compared to control.
EFFECTS ON SPLEEN			
Albino rats (n=30) [55]	14 days, 4mg/kg *bw*	Intraperitoneal	MSG showed adverse effects on the spleen but did not cause permanent damage and reversible in the spleen, and less atrophy was found after MSG was stopped.

Animal Model	Duration and dosage of MSG	Administration Route	Results
EFFECTS ON BEHAVIOR, LEARNING AND MEMORY			
Albino rats (n=40) [47]	30 days, 8 mg/kg *bw* MSG and/or 32 mg/kg *bw* ASM	Intraperitoneal	Exposure to both MSG and ASM decreased locomotor activity and neuromuscular coordination (grip strength): increased non-social behavior by causing many disorders in fear and anxiety behavior in each group; and reduced the perception of attack and biting in case of a threat. Also, motor activities and neuromuscular transmission have been disturbed.
Male Wistar Albino rats (n=30) [14]	60 days, 100 mg, 400 mg, 2 or 4 g/kg *bw*	Oral	Immediately after 60 days of MSG reduced T-maze response and discrimination index in the NOR test and an increase in body weight and AchE level without dose-dependent. However, the changes were statistically significant in the group receiving 4 g/kg *bw*/daily MSG supplement.
EFFECTS ON COAGULANT SYSTEM			
Male rats (n=16) [54]	14 days, 4.40, 6.64 or 13.28 g/kg *bw*	Oral gavage	The doses of 6.64 and 13.28 g/kg *bw*/daily of MSG significantly increase platelet cell counts, platelet count, bleeding time, and clotting time.
EFFECTS ON ANEMIA			
Pigs (n=12) [53]	30 days, 10 g/kg *bw*	Oral	MSG increased serum iron level and iron-binding capacity.
EFFECTS ON METABOLOMICS			
Newborn pigs (n=48) [56]	21 days, 0.03, 0.25 or 0.50 g/kg *bw* twice daily	Oral	Serum trimethylamine and decreased unsaturated fat content increased, whereas serum citrate content decreased at the end of 7 days in the group receiving 0.5 g/kg MSG. After 21 days, the nitrogen content of glutamine, trimethylamine, albumin, choline, urea, and GLP-1 increased, and creatinine content decreased. Serum leptin level was found at the lowest level in this group.
Wistar rats [57]	2 weeks, 1 g% of MSG	Oral	Trimethylamine in kidney increased.
EFFECTS ON MICROBIOTA			
Pigs (n=32) [58]	30 days, up to 3% of dietary fat	Oral	MSG increases in the populations of *Faecalibacterium prausnitzii* and *Roseburia* species.
Rats (n=20) [59]	14 days, 1 g % of MSG	Oral	MSG decreased *Bifidobacterium* species.

MSG: monosodium glutamate, ASM: aspartame, mg: milligram, g: gram, kg: kilogram, mL: milliliter, bw: body weight, ZF: zona fasciculata, ALT: alanine aminotransferase, AST: aspartate, aminotransferase, ALP: alkaline phosphatase, Hb: hemoglobin, MCHC: mean erythrocyte, hemoglobin concentration, TC: total cholesterol, TG: total triglyceride, MDA: malondialdehyde, HDL: high-density lipoprotein, LDL: low-density lipoprotein, GST: glutathione s-transferase, GSH: glutathione, SOD: superoxide dismutase, CAT: catalase, NO: nitric oxide, NMDAR: methyl-D-aspartate receptor, AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor, ChE: cholinesterase, CPK: creatine phosphokinase, CPK-BB: creatine phosphokinase isoenzymes BB, PTX: paclitaxel, NOR: novel object recognition test, AchE: acetylcholinesterase, GLP-1: glucagon-like peptide-1.

Also, the highest serum insulin level was found in the MMG group. Cholecystokinin (CCK) level was lower in HMG group than LMG group. MSG supplementation after 21 days, the nitrogen content of glutamine, trimethylamine, albumin, choline, and urea significantly increased while the creatinine content decreased in HMG group. In addition, glucagon-like peptide-1 (GLP-1) content was found to be the highest level, whereas leptin levels were at the lowest in the HMG group. CCK content was at the highest level in MMG group [56]. Another study observed that trimethylamine in the kidney increased with MSG supplementation in rats [57].

The microbiota is a community of microorganisms known as the "forgotten organ" that contributes to many factors such as health protection, disease prevention, or treatment [5]. Only two preclinical studies were found evaluating the effect of MSG on the microbiota. MSG supplementation of up to 3% of dietary fat for 30 days led to an increase in the populations of *Faecalibacterium prausnitzii* and *Roseburia* species in pigs [58]. Additionally, 1 g% MSG for 2 weeks decreased *Bifidobacterium* species in rats [59]. Future studies will clarify MSG exposure due to the fact that metabolomics and microbiota are up-to-date issues, and there are very limited studies on these issues

3.2. Clinical studies on MSG exposure.

Clinically, the effects of MSG consumption on appetite and obesity have been mainly evaluated. In addition to these effects, the results of studies show that MSG exposure is associated with taste perception, pain symptoms, nervous system, and microbiota (Table 2 and 3).

3.2.1. Effects on food and energy intake.

Due to its increasing tendency to use MSG as a food additive, it is expected to increase food palatability by reducing satiety [1], but clinical studies conducted on this subject are contradictory.

450 mL of carrot soup was prepared as low-energy, high-energy, or high-carbohydrate and -protein with added 0.6% MSG and 0.25% inosine 5 monophosphate (IMP) or without added MSG and IMP were consumed on 4 nonconsecutive days after 3 hours after breakfast. When the appetite levels of participants at lunch were examined, a higher rate of decrease in food intake was observed in those who consumed MSG/IMP added to soup compared to those who consumed without MSG/IMP added to the soup. Added MSG/IMP increased soup satisfaction and caused an immediate increase in appetite when the soup was first tasted [60]. Similarly, male adults consumed carrot soup (500 mL) with the addition of 5 g MSG, 36 g protein, or both, and it was concluded that MSG supplementation increased fullness and reduced appetite [61]. It was found that after consuming 3.8 g of MSG added to the vegetable broth for 4 weeks, the participants' desire for and intake of savory food reduced [62]. In another study, women were divided into 4 groups: base chicken broth, 1.19 g MSG added chicken broth, 0.03 nucleotide and 1.22 g MSG added chicken broth and fat added chicken broth; and the preloads were exhibited twice at 09.00 and 11.15 hours for a maximum cumulative dose of 2.44 g MSG. Motivation ratings were measured before and 15 minutes after ingestion for a total of 210 minutes. Test lunch was served at 12:00, and plate waste was measured. As a result of the study, chicken broth with MSG did not increase energy intake at lunch or did not affect

motivational ratings over the entire testing session. MSG supplementation has been found to reduce hunger and the desire to snack [63].

The effects of MSG on appetite have also been evaluated in infants. Infants were divided into three groups, the first group was fed with an isocaloric formula low in free amino acids (cow milk formula; CMF), the second group was fed with a formula high in free amino acids (extensive protein hydrolysate formula; ePHF) and the third group was fed with CMF added 84 mg/100 mL glutamate. When infants signaled hunger again, they were fed a second meal of CMF. This procedure was repeated 3 times to consume each food. Infants who were fed with CMF+glutamate or ePHF found higher satiety levels and satiety ratio compared to CMF group [64].

Some studies conclude that MSG supplements do not affect appetite. For example, healthy adults have supplemented 2 g/daily of MSG or sodium chloride (NaCI) for 6 days; and on the 7th day, they consumed the same liquid standard meal with MSG or NACI. MSG supplementation was found to have no significant effect on hunger and fullness, body weight, urea concentration, plasma glucose, insulin, GLP-1, and ghrelin levels compared to NACI supplemented group [65]. In another study, carrot soup (450 mL) was prepared with different MSG concentrations (1% MSG added or no MSG) and low-energy control, high-energy carbohydrate or high-energy protein; and participants' appetite levels at lunch were recorded. Consumption of carrot soup with high-energy protein was observed to reduce food intake at lunch compared to those who consume high-energy soup and provide a more accurate energy balance. Especially in soups with high-energy protein and MSG added, this difference was observed more clearly, but no significant difference was found in macronutrient intake. The study indicated that high protein and MSG added nutrients might improve energy compensation [66].

Many studies have shown that MSG supplementation increased satiety and decreased appetite, food intake and hunger [60-64]. Some studies have reported that it does not affect appetite and does not have a significant effect on hunger or macronutrient intake [65,66]. Along with the ability of MSG to increase saliva secretion and affect carbohydrate metabolism, contradictory results may have been found due to its effect on hunger and satiety depending on meal composition, but long-term and involving large numbers of participants, clinical studies are needed to evaluate MSG effects on metabolism. In addition, clinical studies with a high number of participants are needed to clarify the effects of the long-term exposure to MSG on satiety and food intake with body weight and body mass index (BMI).

3.2.2. Effects on obesity.

Obesity has an increasing prevalence all over the world, bringing along many chronic diseases, such as increases in the risk of DM, MetS, CVD by disrupting glucose and lipid metabolism. While it is more common in preclinical studies that MSG supplementation can cause obesity [13-17], less risk is determined in clinical studies [67,68]. Besides, some studies have been reported no effect on obesity [69,70].

In a study conducted with mildly obese or obese individuals, MSG and other nutrient consumptions were assessed with three 24-h recalls method for 5.5 years, and the mean MSG consumption was found 2.2 ± 1.6 g/daily, which was shown to be associated with an increase in BMI [67].

Table 2. Summary of clinical studies on MSG impact on appetite and energy metabolism.

Participants	Vehicle for MSG	Study Protocol	Results
35 women (20-40 years) [63]	Chicken broth	Volunteers were divided into 4 groups: base chicken broth, 1.19 g MSG added chicken broth, 0.03 nucleotide, and 1.22 g MSG added chicken broth and fat added chicken broth; and the preloads were exhibited twice at 09.00 and 11.15 hours for a maximum cumulative dose of 2.44 g MSG. Motivation ratings were measured before and 15 minutes after ingestion for a total of 210 minutes. Test lunch was served at 12:00, and plate waste was measured.	MSG did not increase energy intake affects motivational ratings over the entire testing session. MSG reduced hunger and desire to snack.
13 adults (30-50 years) [65]	Capsule	Adults supplemented 2 g MSG or NaCI for 6 days, and on the 7th day, they consumed the same liquid standard meal with MSG or NACI	MSG was found to have no significant effect on hunger and fullness, body weight, urea concentration, plasma glucose, insulin, GLP-1, and ghrelin levels.
30 infants (1-3.7 months) [64]	Cow milk formula	Infants were divided into three groups, the first group was fed with an isocaloric formula low in free amino acids (cow milk formula; CMF), the second group was fed with a formula high in free amino acids (extensive protein hydrolysate formula; ePHF) and the third group was fed with CMF added 84 mg/100 mL glutamate. When infants signaled hunger again, they were fed a second meal of CMF.	It was determined that satiety levels and satiety ratio increased in the groups receiving glutamate.
26 adults (18-34 years) [60]	Carrot soup	3 hr after standardized breakfast, volunteers received carrot soup: (1) low-energy, (2) high-energy, (3) high-carbohydrate, (4) high-protein with added 0.6% MSG and 0.25% inosine 5 monophosphate (IMP) or without added MSG and IMP. Changes in appetite during soup intake and at a subsequent (after 45 min) ad libitum lunch were recorded.	Added MSG/IMP decreased food intake and increased soup satisfaction and caused an immediate increase in appetite when the soup was first tasted.
35 adults (18-28 years) [66]	Carrot soup	3 hr after standardized breakfast, volunteers received carrot soup: (1) low-energy, (2) high-energy, (3) high-carbohydrate, (4) high-protein with added 1% MSG or without MSG. Changes in appetite during soup intake and at a subsequent (after 45 min) ad libitum lunch were recorded.	Consumption of carrot soup with high-energy protein has been observed to reduce food intake at lunch compared to those who consume high-energy soup and provide a more accurate energy balance. Especially in soups with high-energy protein and MSG added, this difference was observed more clearly, but no significant difference was found in macronutrient intake; the study indicated that high protein and MSG added nutrients might improve energy compensation.
52 men (20-30 years) [61]	Carrot soup	Volunteers were divided into 5 groups: (1) water (control), (2) carrot soup, (3) carrot soup + 5 g MSG (1% w/w), (4) carrot soup + 36 g net protein, and (5) carrot soup + 36 g net protein + 5 g MSG (1% w/w). Changes in appetite and food intake were recorded at a pizza meal at 120 min.	MSG increased fullness and reduced appetite.
58 adults (16-28 years) [62]	Vegetable broth	Participants consumed 1 cup (237 mL) of low-glutamate (3.8 g MSG) vegetable broth for 4 weeks.	MSG decreased the desire for and intake of savory food.

MSG: monosodium glutamate, IMP: inosine 5 monophosphate, g: gram, mL; milliliter, GLP-1: glucagon-like peptide-1

In another study, families were provided MSG for use in meal preparation for 10 days, and MSG consumption was found 4.0±2.2 g/daily. MSG intake increased the prevalence of MetS and BMI in a dose-dependent manner, independent of total energy intake and level of physical activity. Every 1 g increase in MSG intake significantly increased the prevalence of MetS by 1.4-fold and overweight by 1.16-fold [68].

There are also studies showing no significant relationship between weight gain and MSG consumption. In one study, participants' food consumption records were collected in 2002 and followed up on in 2007, and MSG consumption was found to be unrelated to significant weight gain after controlling for age, gender, multiple lifestyle factors, and energy intake factors [69]. Similarly, the average MSG consumption of the participants whose food consumption was recorded for three 24-hour recall methods was found 2.2±1.8 g/daily. It has been reported that the prevalence of overweight participants was 27.9%, and 81% of them consumed MSG, but when assessing MSG intake after adjustment for age, gender, multiple lifestyle factors, and energy intake, there was no significant association between weight gain and MSG consumption [70].

Clinical studies were not planned supplementation of MSG but were planned to determine the relationship of the mean doses of MSG consumption with body weight, BMI, obesity, and MetS prevalence through food consumption records. These studies show that MSG consumption is likely to cause obesity by increasing BMI. Considering that MSG consumption causes weight gain in most preclinical studies, the effect of MSG consumption on weight gain should be evaluated in the context of ethical values, as in preclinical studies, rather than the relationship between MSG consumption and obesity. Therefore, more studies are needed to conclude whether it accurately causes obesity.

3.2.3. Effects on pain symptoms.

Although clinical studies on pain-associated conditions do not provide strong results, studies showed that MSG consumption improves headache and migraine symptoms, but strong clinical evidence in support of such claims is lacking (Table 3).

Fibromyalgia and temporomandibular disorders are muscle group diseases; patients are characterized by recurrent muscle and headaches [71,72]. The administration of MSG and aspartame-free meals for 4 weeks decreased pain symptoms associated with fibromyalgia and increased quality of life which decreased due to irritable bowel syndrome (IBS) [71]. In contrast, in another study, MSG-free meals for 3 months did not reduce fibromyalgia pain [73]. The results of a randomized, double-blinded, placebo-controlled study found that oral administration of MSG with 150 mg/kg in myofascial temporomandibular disorder (TMD) patients increased in headache after 15 minutes, even 30 minutes, this rate was 40% [72].

According to the results of the studies, although MSG is thought to be a possible triggering agent for pain types, including headache and pain associated with fibromyalgia, studies are limited, but the results also show that there may be a connection between MSG and pain symptoms, and MSG-free diets in such patients may be beneficial for therapeutic purposes.

3.2.4. Effects on the nervous system.

Neurodegenerative diseases are one of the most important health problems of the elderly population. There has been no clinical study on this subject, but studies on *in vitro*

human neuron cells, which we have included in this review to provide information, have shown that MSG supplementation is one of the important risk factors in neurodegeneration (Table 3). Preclinical studies support these results (Table 1).

Oxidative stress is considered the primary reason for many diseases such as neurodegeneration. A study that determined the adverse effects of MSG in neuronal cells line IMS-2 found that GSH, SOD, CAT activities, and total protein levels were significantly reduced in human neuroblastoma IMR-32 cells after 7 mM of MSG [74]. In another study, MSG supplementation significantly increased lipid peroxidation and protein carbonyl formation along with the impairment in antioxidant defense mechanism also, 1.7 mM of MSG resulted in 91% cell viability whereas 3.5 mM and 7 mM of MSG resulted in 50% and 79% cell viability in IMR-32 cell line, respectively [75].

Dementia is a cognitive disorder that occurs especially in the elderly. Nutrition is thought to be effective in preventing dementia in recent years. In a study, patients with dementia consumed MSG with the dose of 0.9 g/three times a day for 12 weeks, and MSG intake did not cause a significant difference in the scores of the Touch Panel-type Dementia Rating Scale (TDAS) and Gottfries-Brane-Steen Scale (GBSS), but concerning the TDAS subtitles "the accuracy of the order of a process", was not adversely affected and remained constant in the MSG group compared to the control. TDAS total scores in the MSG group improved statistically significantly compared to the control group at the 4-week follow-up assessment. Additionally, a correlation was found between TDAS and the meal's enjoyment. MSG supplementation showed greater improvement in cognitive functions. These results showed that MSG could be used for therapeutic purposes in dementia patients [76].

Although these results showed that MSG supplementation negatively affected the nervous system, it is very difficult to evaluate the exact effect on the nervous system clinically. In preclinical studies, exposure to MSG altered the morphological structures of the brain, hippocampus and cerebellum, and antioxidant defenses in the brain. Considering the negative effects and the seriousness of the results, it is very important to verify these issues with clinical studies. Moreover, a clinical study showed that it can be used for therapeutic purposes in dementia patients. However, there is no other study about this issue. Therefore, more clinical studies are needed to clarify the relationship between MSH exposure and dementia.

3.2.5. Other effects related to MSH exposure.

One possible factor related to the prevalence of obesity is the response to the taste of food, which is an important determinant of palatability and intake. In a study, it was evaluated whether MSG (29 mmol/L) supplementation at a 2-day study separated by 1 week showed altering the perception of umami and sweet taste in women. It was found that obese women need higher concentrations of MSG to detect a taste [77]. The study showed that MSG consumption is associated with body weight. Additionally, a recent study observed that adding MSG enhanced saltiness, particularly in the 0.3% NaCl solution, while the effect was attenuated in the 0.6% and 0.9% NaCl solutions [78]. Further studies are needed to assess the mechanisms between them.

A clinical study on microbiota was found, and it was reported that MSG supplementation with 2 g/daily for 4 days did not show a significant difference in the structure of the microbiota [4]. As it is known, the intestinal microbiota composition and the regions where some nutrients are metabolized differ from humans in different animal models [5].

Table 3. Summary of clinical studies associating MSG exposure.

Participants	Study protocol	Results
EFFECTS ON OBESITY		
1277 adults (>20 years) [69]	The food frequency questionnaire was recorded in 2002 and followed up in 2007.	The mean MSG consumption was 3.8 g/daily, and MSG intake was found to be unrelated to significant weight gain after adjusting for age, gender, multiple lifestyle factors, and energy intake factors.
10.095 adults (18-65 years) [67]	MSG and other nutrient consumptions were assessed with three 24-h recalls method for 5.5 years.	The mean MSG consumption was found 2.2±1.6 g/daily, and MSG was associated with BMI.
349 adults (33-55 years) [68]	Families were provided MSG for use in meal preparation for 10 days.	The mean MSG consumption was 4.0±2.2 g/daily. MSG intake increased the prevalence of MetS and BMI in a dose-dependent manner, independent of total energy intake and level of physical activity. Every 1 g increase in MSG intake significantly increased the prevalence of MetS by 1.4-fold and overweight by 1.16-fold.
1528 adults (≥20 years) [70]	MSG and other nutrient consumptions were assessed with three 24-h recalls methods.	The mean MSG consumption was found 2.2±1.8 g/daily. The prevalence of overweight participants was 27.9% and 81% of them consumed MSG, but when assessing MSG intake after adjustment for age, gender, multiple lifestyle factors, and energy intake, there was no significant association between weight gain and MSG consumption.
EFFECTS ON PAIN SYMPTOMS		
57 adults with fibromyalgia and IBS (18-75 years) [71]	MSG and ASM-free meals for 4 weeks.	Diet decreased pain symptoms associated with fibromyalgia and increased quality of life which decreased due to IBS.
72 women with fibromyalgia (24-65 years) [73]	MSG-free meals for 3 months.	Diet did not reduce fibromyalgia pain.
12 adults with TMD (20-38 years) [72]	Single-dose, 150 mg/kg MSG or 24 mg/kg NaCl in 400 mL unsweetened soda	MSG increased in headache after 15 minutes, even 30 minutes; this rate was 40%.
EFFECTS ON NERVOUS SYSTEM		
Human neuroblastoma IMR-32 cell line* [74]	24 h, 7 mM MSG	GSH, SOD, CAT activities, and total protein levels were significantly reduced. MSG increased the mean DNA tail 2.31±0.28%; It reduced the rupture of the DNA head by 89.44±0.14%.
Human neuroblastoma IMR-32 cell line* [75]	24 h, 1.7, 23.5 or 7.0 mM MSG	While SOD, GSH, CAT, and total protein decreased depending on the dose, carbonyl protein and lipid peroxidation increased. Dead cell ratio was 50.8%, apoptosis was 46.0 ± 1.5% in 7.0 mM MSG supplementation, while necrosis was 22.3 ± 1.0%.
137 elderly with dementia (the mean age 86.5±0.75 years in MSG group, 87.8±0.65 years in control group) [76]	12 weeks, 0.9 g MSG or 0.26 g NaCl (3 times a day)	MSG did not cause a significant difference in the scores of TDAS and GBSS, but concerning the TDAS subtitles, "the accuracy of the order of a process", was not adversely affected and remained constant in the MSG group compared to the control. TDAS total scores in the MSG group improved statistically

Participants	Study protocol	Results
		significantly after 4 weeks when compared to the control group and a correlation was found between TDAS and the enjoyment of the meal. MSG showed greater improvement in cognitive functions.
EFFECTS ON TASTE OF FOOD		
57 women (23 obese, 34 normal weight) (21-40 years) [77]	29 mmol / L MSG or NaCl on first test day, sucrose on second test day.	MSG showed altering the perception of umami and sweet taste. Also, obese women need higher concentrations of MSG to detect a taste.
561 adults (64 men, 497 women) (19–86 years) [78]	0.3%, 0.6%, and 0.9% NaCl solutions with or without 0.3% MSG	MSG enhanced saltiness, especially in the 0.3% NaCl solution.
EFFECTS ON MICROBIOTA		
12 adults (22-32 years) [4]	4 weeks, 2 g/daily MSG	MSG did not show a significant difference in the structure of the microbiota

* *in vitro* studies, MSG: monosodium glutamate, ASM: aspartame, NACI: Sodium chloride, mg: milligram, g: gram, kg: kilogram, mL; milliliter, h: hour, BMI: body mass index, MetS: metabolic syndrome, IBS: irritable bowel syndrome, GSH: glutathione, SOD: superoxide dismutase, CAT: catalase, TDAS: Touch Panel-type Dementia Rating Scale, GBSS: Gottfries-Brane-Steen Scale

Therefore, there may be a difference between the results of preclinical studies and clinical studies.

4. Conclusions

MSG was preliminarily identified as a GRAS substance by the FDA and has been repeatedly validated in many food science communities, including JECFA and EFSA. However, in June 2017, EFSA re-evaluated the safety of dietary glutamates and showed that the ADI dose was exceeded in all age groups [1]. This may be due to the fact that MSG consumption, which is one of the food additives added to almost all processed foods, has increased as a result of the changes in the diets, especially since the 20th century, and the development of the food industry, as well as the development of processed foods [5].

Preclinical studies have related to MSG administration with obesity, cardiotoxicity, hepatotoxicity, kidney toxicity, neurotoxicity, anemia, spleen toxicity, alteration of lipid and glucose metabolism, negative effects of fertility, coagulant system, and microbiota. However, clinical studies have focused mostly on MSG effects on appetite and energy expenditure. In addition, MSG administration was associated with obesity, neurotoxicity, and increasing pain symptoms, whereas it did not affect the microbiota. Also, MSG can be used as a therapeutic agent in dementia patients by positively affecting cognitive performance. Biological mechanisms of MSG exposure according to preclinical and clinical studies are shown in Figure 2.

In conclusion, various clinical studies indicated that there was a weak relationship between MSG consumption and chronic human exposure. These studies were poorly informative as they were conducted on high doses that do not consume with levels generally intake from food products. We suggested that clinical and epidemiological studies are needed, but it may bring vital risks when the preclinical study results are considered. Therefore, we think that after MSG dose is obtained with food records for clinical studies, some results can be compared with blood, tissue, or histological samples, and this situation can be better elucidated.

Conflicts of Interest

The authors declare no conflict of interest.

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