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¹Poltava State Agrarian University, Poltava, Ukraine**BIOLOGICAL EFFECTS OF MONOSODIUM GLUTAMATE ON THE KIDNEYS
AND POTENTIAL APPROACHES TO THEIR MITIGATION**

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The study provides a systematic analysis of scientific data on the biological effects of monosodium glutamate and the pathogenetic mechanisms underlying its impact on renal tissue. To achieve this aim, the findings of 41 experimental and review publications selected according to the PRISMA approach in PubMed, Web of Science, Scopus, and Google Scholar were summarised. Attention was focused on the functional, biochemical, molecular, and morphological manifestations of MSG-induced nephrotoxicity. Prolonged exposure to high doses of monosodium glutamate was found to be associated with increased creatinine, urea, and uric acid levels, impaired glomerular filtration, renal autoregulation, salt and water excretion, and regulation of water-electrolyte homeostasis. Oxidative and nitrosative stress is identified as a leading pathogenetic mechanism of injury and is characterised by enhanced lipid peroxidation, malondialdehyde accumulation, and depletion of glutathione and antioxidant enzymes. These alterations are accompanied by activation of pro-inflammatory signalling pathways, suppression of Nrf2, increased expression of NF- κ B and cytokines, and initiation of caspase-dependent apoptosis. At the tissue level, glomerular injury, degeneration and necrosis of tubular epithelium, formation of hyaline casts, interstitial inflammatory infiltration, and fibrosis were described. The roles of the gut-kidney axis, metabolic abnormalities, and the dose- and time-dependent nature of toxicity were analysed. The effects of L-carnitine, protocatechuic acid, apocynin, omega-3 fatty acids, *Nigella sativa*, *Ficus carica*, *Garcinia kola*, *Piper nigrum*, and other nephroprotective agents were summarised. Their protective activity is associated with restoration of redox homeostasis, suppression of inflammation, limitation of apoptosis, and improvement of functional and structural renal parameters. The findings substantiate the biological risks of high and chronic monosodium glutamate consumption and provide a theoretical basis for developing strategies to prevent and correct alimentary nephropathy.

Key words: kidneys, rats, monosodium glutamate, MSG, E621, nephrotoxicity, excretory system, oxidative stress, renal glomeruli, tubular epithelium.

Шевченко К.В., Білаш С.М., Григоренко А.С., Беляєва О.М., Білаш В.П.,**Онїпко В.В., Поспєлов С.В.****БІОЛОГІЧНІ ЕФЕКТИ ВПЛИВУ ГЛУТАМАТУ НАТРІЮ НА НИРКИ
ТА МОЖЛИВІ ЗАСОБИ ЇХ КОРЕКЦІЇ**

У роботі представлено систематичний аналіз наукових даних щодо біологічних ефектів глутамату натрію та патогенетичних механізмів його впливу на ниркову тканину. Для досягнення цієї мети узагальнено результати 41 експериментальної та оглядової публікації, відібраних відповідно до принципів PRISMA у базах даних PubMed, Web of Science, Scopus та Google Scholar. Основну увагу приділено функціональним, біохімічним, молекулярним і морфологічним проявам нефротоксичності, індукованої натрію глутаматом. Встановлено, що тривалий вплив високих доз глутамату натрію асоціюється з підвищенням рівнів креатиніну, сечовини та сечової кислоти, порушенням клубочкової фільтрації, ниркової ауторегуляції, екскреції солей і води, а також регуляції водно-електролітного гомеостазу. Окиснювальний і нітрозативний стрес визначено як провідний патогенетичний механізм ушкодження, що характеризується посиленням перекисного окиснення ліпідів, накопиченням малонового діальдегіду та виснаженням глутатіону й антиоксидантних ферментів. Ці зміни супроводжуються активацією прозапальних сигнальних шляхів, пригніченням Nrf2, підвищенням експресії NF- κ B і прозапальних цитокінів, а також запуском каспазозалежного апоптозу. На тканинному рівні описано ушкодження клубочків, дегенерацію та некроз епітелію ниркових каналців, утворення гіалінових циліндрів, інтерстиціальну запальну інфільтрацію та фіброз. Проаналізовано роль осі «кишечник-нирки», метаболічних порушень, а також дозо- та часозалежного характеру токсичної дії. Узагальнено дані щодо впливу L-карнітину, протокатехової кислоти, апоніну, омега-3 жирних кислот, *Nigella sativa*, *Ficus carica*, *Garcinia kola*, *Piper nigrum* та інших нефропротекторних засобів. Їхня захисна активність пов'язана з відновленням редокс-гомеостазу, пригніченням запалення, обмеженням апоптозу та покращенням функціональних і структурних параметрів нирок. Отримані результати підтверджують біологічні ризики високого та хронічного споживання глутамату натрію та створюють теоретичне підґрунтя для розроблення стратегій профілактики й корекції аліментарної нефропатії.

Ключові слова: нирки, шури, глутамат натрію, MSG, E621, нефротоксичність, видільна система, окиснювальний стрес, ниркові клубочки, каналцевий епітелій.

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Monosodium glutamate (hereinafter also referred to as MSG or E621) is the sodium salt of L-glutamic acid, one of the most abundant amino acids in nature [23]. This compound is widely used in the food industry as a flavour enhancer, imparting a

distinctive savoury taste known as umami, which combines notes of sweetness, sourness, bitterness, and saltiness [11]. Glutamate is naturally present in virtually all foods, including meat, fish, poultry, milk, and vegetables. In general, protein-rich foods such as

milk, cheese, and meat contain relatively large amounts of bound glutamate, whereas most vegetables contain comparatively smaller amounts [6]. E621 is also added to numerous processed foods, including instant soups, crackers, frozen meals, sauces, and dressings [23].

Despite its widespread use and general recognition as safe at low doses, international regulatory bodies have established recommended intake limits. The European Food Safety Authority (EFSA) has established an acceptable daily intake of 0–30 mg/kg body weight/day [39]. At the same time, some regulatory authorities, including the Turkish Food Codex, set a maximum permissible concentration of MSG in food products at 10 g/kg [22]. The generally recommended daily intake of MSG is 30 mg/kg body weight/day.

However, studies of actual dietary exposure indicate that these limits are frequently exceeded, particularly in street-vended foods. For example, in Ghana, the concentrations of monosodium glutamate in street-food samples, including noodles (19.64 g/kg) and fried rice (19.52 g/kg), exceeded the Codex Alimentarius recommended limit of 10 g/kg [34].

Despite the widespread use of monosodium glutamate, numerous preclinical studies have raised concerns about its potential adverse effects on health, including its ability to induce metabolic alterations that may contribute to obesity, liver injury, central nervous system damage, and reproductive dysfunction [26].

Chronic and/or excessive exposure to monosodium glutamate has been associated with a broad spectrum of adverse effects, including neurotoxicity, cardiotoxicity, hepatotoxicity, and disturbances of lipid and glucose metabolism [40].

The systemic toxicity of monosodium glutamate is further supported by its ability to induce multiorgan toxicity in Wistar rats, including marked alterations in markers of renal function as well as abnormalities associated with cardiac and neurological function [20]. The kidneys are among the principal target organs because they are responsible for blood filtration, elimination of metabolic waste products, and maintenance of water and electrolyte homeostasis. Therefore, assessment of the effects of MSG on the excretory system should integrate functional, biochemical, and morphological parameters.

Excessive MSG intake has been associated with metabolic disturbances and cytotoxicity. In vitro studies have demonstrated that monosodium glutamate exerts a pronounced dose-dependent cytotoxic effect on the Caco-2 cell line and may also impair fat digestion and alter proteolysis [8]. In experimental animals, MSG exposure has been associated with obesity, increased body weight, insulin resistance, and alterations in somatostatin and insulin secretion [25].

Early-life exposure to monosodium glutamate has been reported to impair growth and induce obesity and hyperinsulinaemia, which may manifest in adulthood as peripheral insulin resistance, increased fibrosis, and reduced muscle mass [41].

In a study by Ati UB et al. (2025) [12], the effects of MSG exposure in adult and neonatal

animals were broadly similar: in both models, MSG was associated with altered body-weight regulation and dyslipidaemia, increased susceptibility to anaemia, and tissue inflammation. Monosodium glutamate significantly ($p < 0.05$) exacerbated depression-like behaviour induced by social defeat stress and anxiety-like behaviour in mice. It also significantly ($p < 0.05$) aggravated deficits in social interaction and increased blood glucose and corticosterone levels in mice exposed to social defeat stress.

Findings of increased creatinine, urea, and uric acid levels are particularly relevant to understanding the nephrotoxicity of monosodium glutamate, as they may indicate impaired glomerular filtration and renal excretory function [7, 32]. Prolonged exposure to high doses of MSG may also be accompanied by reduced renal sodium and water excretion and impaired renal autoregulation [38].

One of the principal mechanisms implicated in MSG-induced renal injury is oxidative stress, manifested by increased lipid peroxidation and reduced activity of antioxidant enzymes [1, 3, 5]. These processes are accompanied by inflammatory responses and activation of apoptotic pathways [21, 26]. The functional and molecular abnormalities reported in these studies are consistent with morphological changes in the glomeruli and tubules, interstitial inflammatory infiltration, and signs of fibrosis [2, 17, 19]. Accordingly, assessment of the renal effects of monosodium glutamate requires integrated consideration of metabolic, biochemical, and structural alterations.

The purpose of the study was to summarize current scientific evidence on the biological effects of monosodium glutamate and to analyse the pathogenetic mechanisms underlying its effects on the kidneys.

Materials and methods. A systematic review of the scientific literature was conducted to provide a comprehensive synthesis of current evidence on the biological effects of monosodium glutamate and to analyse the pathogenetic mechanisms underlying its effects on renal tissue and other organs of the excretory system. The literature search was conducted in PubMed, Web of Science, Scopus, and Google Scholar. The final search was performed on 7 August 2026.

Publications published between 2021 and 2026 were eligible for inclusion in the reference list. Sources published before 2021 were excluded, except for historically important information that, where necessary, could be mentioned in the main text. The analysed literature comprised full-text original experimental studies and review articles published in peer-reviewed scientific journals in English and Ukrainian.

The search strategy included the following terms and their combinations: monosodium glutamate, MSG, E621, rat kidneys, renal morphology, nephron, renal corpuscle, tubular system, renal filtration barrier, excretory system, experimental rat models, nephrotoxicity, renal function, creatinine, urea, uric

acid, glomerular filtration, water and electrolyte homeostasis, oxidative and nitrosative stress, lipid peroxidation, antioxidant system, inflammation, apoptosis, Nrf2, NF- κ B, gut microbiota, gut–kidney axis, and nephroprotective intervention.

The inclusion criteria comprised full-text peer-reviewed publications reporting reliable experimental data on functional, biochemical, molecular, or morphological renal changes associated with monosodium glutamate exposure, as well as findings concerning the mechanisms of nephrotoxicity and potential approaches to its mitigation. Conference abstracts, non-peer-reviewed preprints, duplicate publications, studies without a DOI, and studies not

directly related to renal tissue injury, impaired excretory function, or systemic mechanisms of MSG toxicity were excluded.

As this study was a theoretical review based on publicly available scientific information, approval by a bioethics committee was not required.

Study selection followed the PRISMA approach. At the initial stage, 303 publications were identified. No duplicates were detected during bibliographic screening; therefore, all 303 records underwent title and abstract screening. Subsequently, 74 full-text articles were assessed for eligibility, and 41 publications were ultimately included in the review (Table 1).

Table 1

Simplified PRISMA Flow

Stage	Description	Number of Records / Studies
1. Identified	Total number of records found in scientometric databases using keywords related to monosodium glutamate and renal toxicity	303
2. Duplicates Removed	Number of identical publications removed before screening began	0
3. Screened (Title/Abstract)	Number of records screened by title and abstract after duplicate verification	303
4. Assessed for Eligibility (Full-text)	Number of full-text articles analysed for compliance with methodological criteria and the presence of relevant functional, biochemical, molecular, or morphological data	74
5. Included in Review	Total number of scientific publications finally included in the systematic review and used in the text of the article	41

Results of the study and their discussion. The kidney is the principal organ of the excretory system targeted by MSG-induced toxicity. Chronic exposure to monosodium glutamate has been associated with renal toxicity manifested by biochemical, histological, and functional abnormalities.

The most evident biochemical indicators of impaired renal excretory function are substantial increases in serum markers of nitrogen metabolism. Studies have demonstrated significantly elevated serum urea and creatinine levels in animals receiving monosodium glutamate compared with controls [7]. These changes may reflect impaired glomerular filtration and alterations in tubular reabsorptive function. In adult albino rats, monosodium glutamate caused significant increases in serum creatinine, urea, and uric acid levels, indicating disturbances in nitrogen metabolism and renal excretory function [15].

In addition to affecting the elimination of metabolic waste products, monosodium glutamate may disrupt complex mechanisms of renal autoregulation. Prolonged administration of high-dose MSG (320 mg/kg) was shown to significantly reduce renal sodium and water excretion while simultaneously increasing renal blood flow and glomerular filtration rate [38]. These findings suggest impairment of the autoregulatory mechanisms involved in maintaining glomerular filtration following prolonged exposure to high doses of MSG. Thus, the nephrotoxicity associated with monosodium glutamate may involve a substantial vasorenal component mediated by oxidative stress

and inflammation rather than being attributable solely to direct parenchymal injury.

MSG exposure is also associated with alterations in the regulatory mechanisms governing water and electrolyte balance. In the kidneys of lactating rats, dysregulation of key hormonal receptors and channels was observed: prolactin receptor expression was significantly reduced, whereas oxytocin receptor and aquaporin-3 (AQP3) expression increased significantly [16]. Such alterations may directly affect renal function and the ability of the kidneys to maintain water and electrolyte homeostasis. It should be emphasized that although biochemical markers of nitrogen metabolism are widely used indicators of renal dysfunction, their elevation may reflect relatively advanced injury. By contrast, molecular biomarkers of acute kidney injury, such as neutrophil gelatinase-associated lipocalin (NGAL), may be more sensitive for detecting early renal damage [2, 20].

MSG-induced renal injury is not limited to direct cellular damage but appears to involve multiple interconnected processes, including increased oxidative stress and inflammation [38]. These mechanisms contribute to structural and functional renal abnormalities, with the severity of toxicity frequently showing a dose-dependent pattern.

MSG-induced renal injury is closely associated with oxidative stress, which promotes lipid peroxidation and damage to essential cellular macromolecules [26]. In renal tissue, monosodium glutamate increases oxidative damage and tissue degeneration, as demonstrated by elevated

malondialdehyde (MDA), a major marker of lipid peroxidation, and increased myeloperoxidase (MPO) activity. These changes are accompanied by reduced glutathione (GSH) levels and decreased superoxide dismutase (SOD) activity [5].

Studies have further demonstrated that monosodium glutamate markedly increases oxidative and nitrosative stress in renal tissue, as reflected by excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). MSG administration increased the rate of superoxide anion radical generation by microsomal monooxygenases, the mitochondrial respiratory chain, and leukocyte NADPH oxidase. In addition, MSG increased the concentrations of peroxynitrite and S-nitrosothiols in renal tissue [1]. This dose-dependent oxidative stress, observed with increasing MSG doses (0.8–3 g/kg), was accompanied by significant increases in renal function markers, including urea, creatinine, and uric acid, as well as increased MDA and nitric oxide (NO) concentrations. At the same time, endogenous antioxidant capacity declined, as reflected by reduced GSH levels and decreased activities of catalase (CAT), SOD, and glutathione S-transferase (GST) [3].

In models of MSG-induced obesity, elevated serum urea and creatinine levels were accompanied by reduced albumin concentrations [32]. High MSG intake in lactating rats also significantly increased serum creatinine levels and was accompanied by increased total, conjugated, and unconjugated bilirubin concentrations [16].

MSG-induced renal dysfunction is closely associated with suppression of key antioxidant defence mechanisms. Monosodium glutamate reduces total antioxidant capacity (TAC) in renal tissue and significantly decreases the activity of major antioxidant enzymes, including SOD, CAT, glutathione peroxidase (GPX), and glutathione reductase (GR) [21]. Depletion of these protective mechanisms is associated with increased cellular injury.

An important molecular indicator of this impairment is reduced expression of the nuclear factor erythroid 2-related factor 2 (Nrf2) gene in renal tissue [21]. Nrf2 is a principal regulator of cellular antioxidant defence; therefore, its suppression indicates impaired ability of renal cells to counteract a toxin-induced oxidative environment, thereby facilitating further inflammatory and apoptotic responses.

Immunohistochemical studies have demonstrated significantly increased renal expression of TNF- α following daily MSG administration, indicating activation of an inflammatory response within the renal parenchyma [38]. This process is frequently associated with activation of nuclear factor- κ B (NF- κ B), a key transcription factor regulating the expression of pro-inflammatory genes [21].

Uncontrolled oxidative stress and inflammation may ultimately trigger apoptosis, resulting in loss of functional renal cells. Monosodium glutamate has been shown to activate apoptotic pathways, as indicated by a significant increase in the Bax/Bcl-2 ratio and caspase-3 expression [18].

In renal tissue, MSG significantly increased caspase-9 expression, a key initiator of the mitochondrial apoptotic pathway, while reducing expression of Bcl-2, an important anti-apoptotic protein [26]. MSG-treated groups also exhibited significantly increased numbers of apoptotic cells compared with controls, supporting the involvement of programmed cell death in the development of nephrotoxicity [2; 20]. Thus, the available evidence supports a sequential pattern of toxic events: ROS/RNS generation $\rightarrow$ impairment of antioxidant defence pathways, including reduced Nrf2 activity $\rightarrow$ inflammatory activation $\rightarrow$ initiation of apoptosis, including increased caspase-9 expression.

The renal effects of monosodium glutamate are multifaceted, involving the glomerular apparatus, tubular system, and interstitial tissue.

Prolonged administration of monosodium glutamate for 30 and 60 days resulted in substantial structural changes in the glomeruli. An increase in mesangial mass was reported, attributable to hypertrophy and hyperplasia of mesangial cells and associated with the development of mesangial proliferative glomerulonephritis [19]. MSG has also been associated with glomerular hypertrophy and proteinuria, indicating impairment of the filtration barrier [13].

In models of MSG-induced obesity, histomorphometric analysis demonstrated significant reductions in kidney weight, glomerular diameter, glomerular tuft area, capsular area, and Bowman's space [28]. Histological examination revealed immature glomeruli, thickening of capillary walls, increased mesangial matrix, and, in some cases, focal glomerular necrosis and crescent formation [28]. These findings are consistent with progressive glomerular injury and inflammation.

The tubular apparatus also undergoes substantial degenerative changes. Monosodium glutamate has been associated with deterioration of renal morphology, including degeneration of proximal and distal tubules and hydropic degeneration of thin tubules [3; 5].

In time-dependent studies, MSG exposure resulted in tubular degeneration with pyknotic nuclei and hyaline casts within the tubular lumina [17]. Following more prolonged exposure (14 days), loss of normal tubular architecture and severe degenerative changes in the epithelial lining were observed [17]. Moreover, MSG intoxication resulted in tubular degeneration accompanied by coagulative necrosis of epithelial cells and deposition of haemosiderin pigment [33].

In ageing rats, monosodium glutamate induced histological changes, including accumulation of hyaline droplets, reflecting protein accumulation associated with impaired tubular reabsorption, tubular pigment deposition, and cytoplasmic vacuolation [30].

The toxic effects of monosodium glutamate also extend to the renal interstitium and vascular compartment. Histological examination of the kidneys revealed pathological changes, including leukocytic inflammatory infiltration, vascular atrophy, and congestion [4]. Vascular congestion, inflammatory cell infiltration, and vascular oedema were also detected in renal tissues [5].

Prolonged MSG exposure was associated with renal fibrosis and reduced glycoprotein content [2, 20]. In adult rats receiving monosodium glutamate, histopathological examination revealed focal interstitial inflammatory infiltrates, cellular and hyaline tubular casts, vascular congestion, and loss of PAS-positive brush borders in proximal tubules [29]. This multifocal pattern of injury is consistent with acute nephrotoxicity that may progress towards chronic nephropathy.

MSG-induced nephrotoxicity may also be mediated through disruption of the gut–kidney axis and alterations in microbial metabolite metabolism. Monosodium glutamate consumption has been associated with substantial changes in the gut microbiome, including increases in bacteria of the genera *Firmicutes* and *Clostridium*, which are involved in trimethylamine (TMA) metabolism, together with reductions in beneficial bacterial populations such as *Bifidobacterium* and *Lactobacillus* [31]. These alterations were associated with reduced pyridoxine content and increased TMA levels in renal tissue [31]. The safety of prolonged exposure to high doses of monosodium glutamate therefore warrants further consideration, particularly in populations at increased risk of kidney disease [31, 37].

Further studies have shown that MSG consumption increases serum trimethylamine N-oxide (TMAO) levels while simultaneously reducing its urinary excretion [27, 31, 37]. Accumulation of TMAO in the circulation correlates with increased urinary excretion of neutrophil gelatinase-associated lipocalin (NGAL), a marker of acute kidney injury. This finding suggests that MSG-associated renal dysfunction may involve impaired elimination of potentially toxic uraemic metabolites in addition to direct oxidative injury [27, 31, 37].

MSG-induced gut dysbiosis has also been characterized by persistent suppression of *Akkermansia muciniphila*, a mucin-producing bacterium [27, 31, 37]. The combined effects of monosodium glutamate and a high-fat/high-fructose (HFF) diet exacerbated dysbiosis, increasing the Firmicutes/Bacteroidetes ratio and urinary p-cresyl sulfate concentrations. These findings indicate

disruption of host–microbial co-metabolism and may be associated with an increased risk of renal injury [35].

Although contrary evidence has been reported suggesting that monosodium glutamate does not significantly affect hepatic or renal metabolites because most glutamate is metabolized in the small intestine [14], the available findings support consideration of MSG as a potential precursor of secondary metabolites relevant to systemic metabolic processes.

Monosodium glutamate consumption induces specific alterations in the urinary metabolic profile that may potentially serve as biomarkers of exposure. MSG has been shown to increase urinary pH and bicarbonate levels in a dose-dependent manner, presumably because excess bicarbonate generated during CO₂ metabolism is excreted in the urine [27, 31, 37].

This MSG-associated alkalinization of urine may affect metabolite reabsorption and result in increased urinary excretion of divalent anionic compounds, including alpha-ketoglutarate, citrate, fumarate, succinate, and glutamate, in experimental animals. Dose-dependent changes in urinary metabolic profiles may therefore have potential utility for assessing MSG exposure in future studies of metabolic syndrome-associated chronic kidney disease [27, 31, 37].

MSG-induced toxicity appears to be dose-dependent. In studies involving doses of up to 3 g/kg, the most pronounced toxic effects, confirmed by biochemical and histopathological changes, were observed in animals receiving the highest dose [3]. These findings highlight the need for further investigation of safe long-term exposure limits.

Age is an important determinant of susceptibility. Experiments in aged mice demonstrated pathological renal changes following MSG exposure, including glomerular hypertrophy and injury to renal tubular cells [13]. A study of subchronic MSG exposure in two-year-old rats, used as an ageing model, revealed histological changes including mineralization, which was dose-dependent in the 3000 mg/kg group, and cytoplasmic vacuolation [30]. Although chronic progressive nephropathy is an age-related background condition in rats, MSG exposure may exacerbate its severity.

Pregnancy and the neonatal period are periods of increased susceptibility to potential nephrotoxic effects. MSG exposure has been associated with adverse renal effects in pregnant rats [9]. Pregnant rats receiving MSG exhibited glomerular necrosis, inflammatory cell infiltration, vascular obstruction, hydropic degeneration, and tubular necrosis [9, 10].

In addition, MSG induced degenerative changes in the renal tissues of both mothers and fetuses [36]. In maternal kidneys, atrophic renal corpuscles and degeneration of the epithelium of Bowman's capsule were observed. The kidneys of fetuses whose mothers

received MSG showed loss of normal architecture, with atrophic or degenerated glomeruli and disrupted renal tubules, including epithelial detachment, suggesting impaired nephrogenesis [36]. In neonatal rats, renal histopathology demonstrated marked interstitial inflammatory infiltration, interstitial haemorrhage, cloudy degeneration of the tubular epithelium, and focal necrosis [29]. These findings suggest that MSG exposure during critical developmental periods may have long-term consequences for renal health.

The toxicity associated with monosodium glutamate may be exacerbated by other metabolic or chemical stressors. Combining MSG exposure with a high-fat/high-fructose (HFF) diet significantly increased the risk of renal injury and exacerbated gut dysbiosis [35]. Toxicological studies have also demonstrated that combined exposure to MSG and methanil yellow (MY) induces hepatorenal injury, with both agents promoting oxidative damage and apoptosis [18]. A particularly pronounced interaction has been reported for combined exposure to monosodium glutamate and sodium nitrite (NaNO_2), which resulted in marked pathological changes, including exacerbated tubular and glomerular necrosis and degeneration in pregnant rats [9, 10].

Although most studies have reported adverse effects, some investigations have yielded different findings. For example, a study examining the effects of MSG on neural stem cells (NSCs) in mice found no evidence of toxicity to NSCs or impairment of hippocampal neurogenesis [24]. Some researchers have also argued that MSG does not induce significant alterations in the gut microbiota or subsequent metabolic changes in the liver or kidneys because it is metabolized predominantly in the small intestine, and that long-term exposure does not pose a health risk. It should be noted, however, that these counterarguments were presented in a commentary on the original article and that the commentary authors received financial support from glutamate manufacturers [14].

Studies in ageing rats have suggested that subchronic MSG exposure may also activate certain protective mechanisms, although hyaline droplets and cytoplasmic vacuolation were observed in renal tissue [30].

Studies of MSG-associated nephrotoxicity have identified a range of agents capable of attenuating its adverse effects, supporting the oxidative pathway as an important therapeutic target.

Several natural compounds have demonstrated nephroprotective potential:

- *Garcinia kola* extracts (*Garcinia kola* methanolic extract (GKME) and *Garcinia kola* aqueous extract (GKAE): These extracts effectively attenuated MSG-induced multiorgan dysfunction and oxidative damage, suggesting potential benefits in reducing MSG-associated toxicity [20].

- *Apocynin*: Apocynin reduced MSG-induced renal injury by modulating the antioxidant–oxidant balance and improving renal histology, although the underlying mechanism requires further investigation [5].

- *Punica granatum* juice (PJ) and *bee pollen* (BP): Co-administration of these nutraceuticals attenuated the toxic effects of MSG, including biochemical and histological renal abnormalities [15].

- *Ficus carica* extract (FC): FC reduced MSG-induced oxidative stress, apoptosis, and histopathological alterations and improved renal function. Its bioactive compounds demonstrated high binding affinity for Bax and caspase-3, suggesting a potential direct anti-apoptotic effect [18].

- *Nigella sativa* seeds (NSS): NSS attenuated MSG-induced renal abnormalities by reducing oxidative stress, normalizing lipid peroxide levels, and exerting anti-apoptotic effects, thereby improving histopathological alterations [2; 20].

- *Piper nigrum* extracts (methanolic extract of *Piper nigrum* (MEPN) and hexane *Piper nigrum* extract (HEPN): These extracts significantly restored SOD and CAT activities and GSH levels, reduced MDA concentrations, and attenuated increases in serum urea and creatinine. Histopathological signs of toxicity, including congestion and necrosis, were also reduced [33].

- *Vernonia amygdalina* extract: This extract significantly reduced elevated serum urea and creatinine levels and attenuated signs of renal toxicity [32].

Molecular modulators and specific nutrients may also contribute to renal protection:

- L-carnitine (L-Ca): L-carnitine exerted a protective effect against MSG-induced renal injury. It significantly reduced MDA, blood urea nitrogen (BUN), creatinine, and uric acid levels and increased the activities of antioxidant enzymes, including CAT, GPX, and SOD [26].

- Protocatechuic acid (PCA): PCA attenuated MSG-induced hepatorenal injury by modulating oxidative, inflammatory, and apoptotic processes. This protective effect was associated with activation of Nrf2 and inhibition of the NF- κ B signalling pathway [21].

- Zinc oxide nanoparticles (ZnO-NPs): ZnO-NPs reduced the adverse effects of MSG by decreasing lipid peroxidation and enhancing intracellular antioxidant defence. They have demonstrated antioxidant, anti-inflammatory, and antifibrotic properties [4].

- Omega-3 fatty acids: Omega-3 supplementation contributed to reductions in serum urea and creatinine levels, indicating a potential protective effect against MSG-associated renal injury [7].

Across these experimental studies, effective nephroprotective strategies generally targeted

restoration of redox homeostasis, reduction of MDA levels, and enhancement of antioxidant enzyme activity. These findings further support oxidative stress as an important pathogenetic mechanism in MSG-associated nephrotoxicity and suggest that modulation of endogenous antioxidant signalling, including the Nrf2 pathway, may be more effective than nonspecific free-radical scavenging alone.

A comprehensive analysis of the effects of monosodium glutamate on the excretory system indicates that MSG can induce functional, biochemical, and structural renal abnormalities through several interconnected molecular mechanisms.

MSG-induced functional impairment is reflected in increased serum creatinine, urea, and uric acid levels. These changes are consistent with impaired glomerular filtration and reduced renal excretory capacity [7, 15]. Impaired renal autoregulation has also been documented, accompanied by reduced renal sodium and water excretion [38]. In addition, disturbances of water and electrolyte balance have been associated with altered AQP3 expression and changes in renal hormonal receptor expression [16].

The underlying renal injury is multifactorial. MSG exposure promotes oxidative and nitrosative stress, characterized by excessive generation of reactive oxygen and nitrogen species [1] and lipid peroxidation, reflected by increased MDA levels,

together with depletion of endogenous antioxidant defences, including GSH, SOD, and CAT [3, 5].

These alterations are accompanied by activation of inflammatory pathways, including increased TNF- α and IL-6 levels, and suppression of the key antioxidant regulator Nrf2 [21]. Ultimately, these processes may activate apoptotic pathways, as reflected by increased caspase-9 expression and an elevated Bax/Bcl-2 ratio [18, 26].

Structural abnormalities include glomerular injury, such as mesangial proliferative glomerulonephritis, glomerular hypertrophy, and focal necrosis [13, 19, 28], as well as tubular injury characterized by necrosis, degeneration, and the presence of hyaline casts [17]. These changes are accompanied by interstitial inflammatory infiltration and fibrosis [2, 4, 20].

Particular attention should be given to the gut–kidney axis because MSG-induced alterations in the gut microbiome may increase the production and reduce the renal elimination of potentially toxic microbial metabolites, including TMAO, and may thereby contribute to acute kidney injury [27, 31, 37].

Importantly, the available evidence indicates that MSG-associated toxicity is dose-dependent [3] and may be more pronounced during vulnerable developmental periods, including pregnancy and the neonatal period, when exposure may interfere with normal nephrogenesis [29, 36].

Conclusion

This systematic review demonstrated that prolonged exposure to high doses of monosodium glutamate is associated with complex functional, biochemical, molecular, and morphological alterations in the kidneys. The principal manifestations of nephrotoxicity include increased creatinine, urea, and uric acid levels, impaired glomerular filtration, altered renal autoregulation, and disturbances of water and electrolyte homeostasis. The major pathogenetic mechanisms underlying renal injury include oxidative and nitrosative stress, depletion of antioxidant defences, activation of inflammatory responses, and apoptosis. These processes are accompanied by structural alterations in the renal glomeruli and tubules, interstitial inflammatory infiltration, and fibrosis. The reviewed evidence also indicates dose- and time-dependent patterns of pathological change and an association with systemic disturbances of lipid and carbohydrate metabolism.

Nephroprotective strategies, including L-carnitine, protocatechuic acid, and extracts of *Ficus carica* and *Garcinia kola*, have demonstrated protective effects in experimental models, primarily through restoration of redox balance and modulation of Nrf2/NF- κ B signalling pathways. Overall, the available evidence indicates that high-dose and prolonged MSG exposure may adversely affect renal health and that its potential renal effects should be considered in the broader context of systemic metabolic dysregulation.

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