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Examination Outcome of Public Uses of Monosodium Glutamate as A Flavor Enhancer On Structural, DNA Content and Nuclear Factor-Kb Expression of Some Organs of Swiss Albino Mice

Sherin Ramadan Hamad*

Associate professor on department of Histopathology. Egyptian Drug Authority Operations and Control Sector (Previously National Organization for Drug Control and Research (NODCAR))

***Corresponding Author:** Sherin Ramadan Hamad, Associate professor on department of Histopathology. Egyptian Drug Authority Operations and Control Sector (Previously National Organization for Drug Control and Research (NODCAR)), E-mail: manaa_82@yahoo.com

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ABSTRACT

Background

Monosodium glutamate is commonly used as flavor enhancer/food additive in protein-rich food like meat, fish, milk and cheese or vegetable origins. Therefore, this current study aimed to evaluate the role of usually uses of monosodium glutamate in histological structure of heart, spleen, liver, and kidney in mice. Twenty animals were divided into two: control group; and glutamate treated group. The experimental period was two successive weeks. Administrations of monosodium glutamate caused histological alterations of all examined tissues and decreased in content of DNA. Significant increase of the nuclear factor-kB expression was also recorded in animal administration monosodium glutamate.

In conclusion

It could be concluded that common uses of monosodium glutamate induced histological lesions and cytotoxicity in heart, spleen, liver, and kidney tissues.

Keywords: Monosodium glutamate; DNA content; Histopathological; Immunohistochemistry; Mice

Introduction

Monosodium glutamate (the salt of glutamic acid) is widely spread as food additives to preserve or enhance of palatability [1]. It is consisted of sodium salt of glutamic acid [2], 78% of glutamic acid, 22% 26 of sodium and water [3]. Monosodium glutamate is metabolized in the liver [4]**.** In nature, glutamate (Glutamic acid) is considered as one of the most common amino acids and is the main component of many proteins and peptides of most tissues [5, 6]. Human body induced glutamate where it has an essential role in metabolism [6], regulating gene expression, cell signaling, ant oxidative responses and immunity [5]. Main sources of glutamic acid are all meats, poultry, fish, eggs, dairy products, tomato and some protein-rich plant foods, hydrolyzed protein such as yeast extract and many fermented or aged foods, including soy sauce, fermented bean paste [7]. Many prepared foods were used glutamate in the form of monosodium glutamate as an additive [8]. Monosodium glutamate, as food additive is recorded on food labels as a "Flavoring". It has ability to ameliorate the meals palatability and induce positive appetite and gain of weight. It is usually used in many food products such as noodles, flavored potato chips, many food snacks, soups, frozen foods and stuffed chicken [2]. In addition to, it greatly utilize within home and food industries, as well as fast foods and restaurant cooking. Meanwhile, consuming of dietary monosodium glutamate in human resulted in different unwanted effects as sweating, muscle pain, fatigue, headache, neuropathy, ventricular arrhythmia, abdominal discomfort, skin reactions and asthma [9, 10]. Similarly, monosodium glutamate induced pathologies in the liver tissues [11], testis of rat [12] and ovaries of either female mice [13, 14] or female rats [15]. The effect of monosodium glutamate, on the retina of rabbit was also studied histologicl and electroretinographic by [16].

The U.S. Food and Drug Administration considers MSG as safe, while the European Union's Food Safety Authority determines an intake of 30 mg/kg body weight per day as safe [17]. However, administration of monosodium glutamate at low concentration resulted in hepatotoxic at dose level 5mg/kg of body weight [18] and renal toxicity at dose level 4mg/kg of body weight [19] as evidences by histological, immumohistochemical and ultrastructure. In addition to, [20] found also that when rat administration with 4 mg/kg of monosodium glutamate for fourteen days, severe spleen damage was recorded and explained by histological findings. Likewise, [21]**,** reported toxicity of monosodium glutamate when administration to rat at dose 3 g/kg body weight (1/5 LD50) daily for 8 weeks in thymic and splenic tissues after prolonged consumption. [22] also recorded the toxic influences of monosodium glutamate in the function of liver tissue in rats. He reported that administration of monosodium glutamate at dose 60 mg/Kg for 4 weeks resulted in the elevation of hepatic enzymes and lipid profile as cholesterol, Triglycerides**.** Likewise, [23] stated that monosodium glutamate at the dose 3 mg /kg body weight induced conspicuous pathological lesions in the liver tissue when it was administrated orally for 45 successive days**.** Neurotoxicity of monosodium glutamate were also evaluated by [24]**.** Therefore, the aim of this paper was designed to study effect of monosodium glutamate on heart, spleen, liver, and kidney tissues of male Swiss albino mice using histopathological, histochemistry and immunohistochemistry studies.

Methods and Materials

Experimental Design

Animals were divided into equal two groups: fist group served as control group, and its animals treated orally with distil water (1ml/kg.bw); second group (Glutamate treated group): mice orally supplementation with monosodium glutamate was orally at dose (4 mg / g body weight) for 14 days according to [19]; The experimental period was two successive weeks. At end of experimental, the animals are euthanized after 24 h of the last dose by decapitation after intraperitoneal injection of Sodium pentobarbital (50 mg /kg) and dissection and heart, spleen, liver and kidney tissues were freshly collected directly and immediately transferred to 10% formalin for fixation to use in histopathological, histochemical and immunohistochemistry studies

Chemicals

Monosodium glutamate was obtained from the Shanghai Bio Life Science & Technology Co., Ltd. (China) while and others chemicals were obtained from Sigma Aldrich (St. Louis, MO, USA).

Animals and Ethics

Animals were obtained from the animal house of National Organization for Drug Control and Research (NODCAR) in Giza, Egypt. In this study, twenty male Swiss albino mice aged 9 – 12 weeks and weighing 25 -30 g were used. Animals were supplied with standard commercial diet pellets and water that *Ad-labium*, kept in plastic cages for 7 days to be accommodated with our laboratory conditions before treatment. All male Swiss albino mice were grouped and housed according to the guidelines of the institutional animal's ethics committee of NODCAR. All the experimental procedures were carried out accordance with international guidelines for the care and use of laboratory animals. All experimental procedures were conducted in accordance with the ethical standards and were approved by the Institutional Animal Care and Use Committee (IACUC) at NODCAR **(approval no.** NODCAR/III/41/2019**)**.

Histological and Histochemical Investigations

After 48 hours from fixation in10% formalin, the specimens of heart, spleen, kidney and liver were washed, dehydrated in ascending grades of alcohol, cleared in xylene and embedded in paraffin wax. [25] Five micron thick paraffin sections were prepared, mounted on clean slides and stained with Ehrlich's haematoxylin-eosin for histological study and Feulgen's reaction to demonstrate DNA content [26].

Immunohistochemical Analysis

NF-κB (nuclear factor-kB) Immunostaining was carried out on the heart, spleen, liver and kidney tissues with PBS have 113 0.05 M EDTA followed by 4% paraformaldehyde. 5-µm sections were incubated with blocking reagent, primary antibody anti-NF-κB (17) in the presence of 10% rabbit serum overnight at 4℃, followed by biotin-conjugated goat anti-rabbit Ig, avidin-linked HRP complex and 3,3'-diaminobenzidine as substrate. For quantification measurement, slides were counterstained with hematoxylin, followed by dehydrated, examined under a light microscope and the intensity of brown color indicator for cell immunopositivity was assessed. These measurements were done using an objective lens of magnification X40, i.e. of total magnification X400. Ten readings were obtained in each specimen using Leica Qwin 500 image analyzer computer system (England) in the faculty of medicine, Cairo University.

Statistical analysis

The experimental data were analyzed using analysis of variance (ANOVA) with GraphPad Prism (version5.00 for Windows), GraphPad Software (CA, USA). $P < 0.01$ is considered to be significant. All calculated data are expressed as mean ± standard deviation (SD).

Results

Histological examination of

Heart tissues

Light microscopic examination of heart tissues from control animal revealed normal cardiac muscle fibers with a centrally arranged nucleus **(Figure 1a)**. On contrast, heart sections from animals treated with monosodium glutamate showed prominent areas of distortion normal structures as evidence by degenerated cardiac muscular fibers; scattered congested dilated blood vessels and edema. Marked degenerative cardiac fibers, necrotic areas and mild aggregation of inflammatory cells were also seen compared to the control group (Figure 1b) compared to control group.

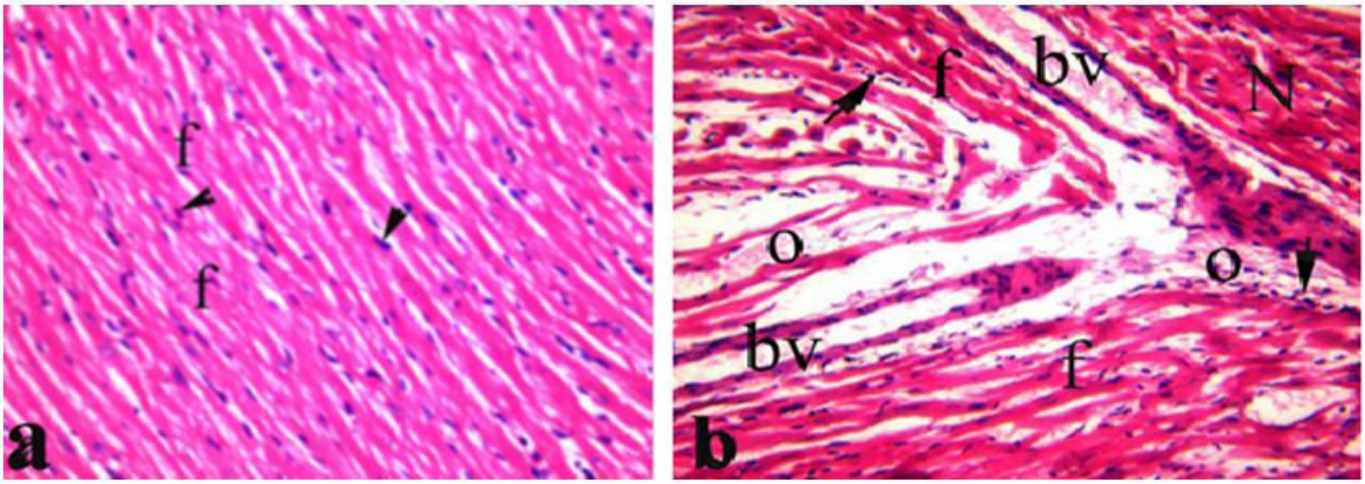

Figure 1: lights photomicrograph of heart section stained with H &E. X200. **(a)** Heart section from control animals showing normal cardiac muscle fibers with a centrally arranged nucleus (f); **(b)** Heart section from monosodium glutamate treated mice showing distortion normal structures as degenerated cardiac muscular fibers (f); scattered congested dilated blood vessels (bv) and edema (o). Necrotic areas (N) and mild aggregation of inflammatory cells (arrow) were also seen

Spleen tissues

Microscopically examination of spleen sections from non-treated mice revealed normal spleen architecture with normal appearance of white pulp and red pulp. White pulp is formed of a large number of lymphocytes surrounding the central arteries and red pulp is formed of reticular cells, red blood cells, lymphocytes, macrophage, and some plasma cells (Figure 2a&b). On another hand, spleen tissues from animal orally administrated with monosodium glutamate showed ill-defined spleen architecture, severe degenerative changes in white pulp and red pulp together with edema, scattered giant cells and diffused degenerated lymphoid cells compared to the control group (Figure 2c1). Another area showed ill-white pulp with numerous necrotic foci filled by darkly stained cell (Figure 2c2).

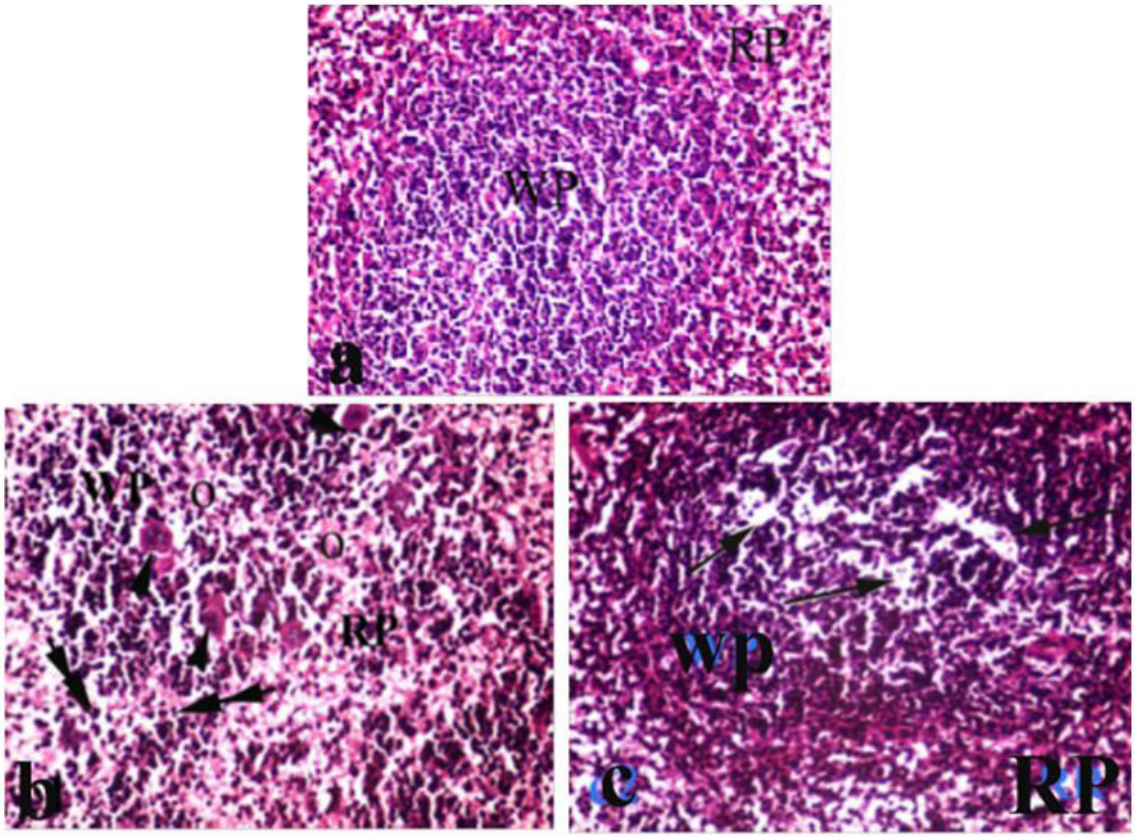

Figure 2: Light photomicrograph of spleen sections stained with H &E. X200. (a). Spleen sections from control animals showing well defined white pulp (WP) and normal appearance of red pulp (RP); **(b)** Spleen sections from monosodium glutamate treated mice showing severe degenerative changes in white pulp (WP) and red pulp (RP) together with edema (o), giant cells (two head arrow) and diffused degenerated lymphoid cells (arrow); **(c)** Spleen sections from monosodium glutamate treated mice showing ill white pulp with numerous necrotic foci filled by darkly stained cell (two head arrow).

Liver tissue

Examination of H & E sections from liver of mice non-treated revealed normal appearing of hepatocyte that radiated from central vein and separated by sinusoids (Figure 3a). In contrast, liver sections from mice administrated monosodium glutamate only showed prominent areas of severe vacuolar degenerative hepatocyte, marked dilated congested central vein accompanied with perivascular mild aggregation inflammatory cells (Figure 3b). Most portal areas revealed marked vacuolar degenerative hepatocyte with pyknotic nuclei, severe dilated, congested portal veins and moderate dilated bile ducts, and perivascular diffused dense aggregation of inflammatory cells (Figure 3c). Another area showed scattered dense inflammatory cells aggregation in hepatic tissues and in sinusoids together with occasionally giant cells (Figure 3d). Necrotic areas, edema and vacuolar degenerative hepatocyte were also seen (Figure 3e).

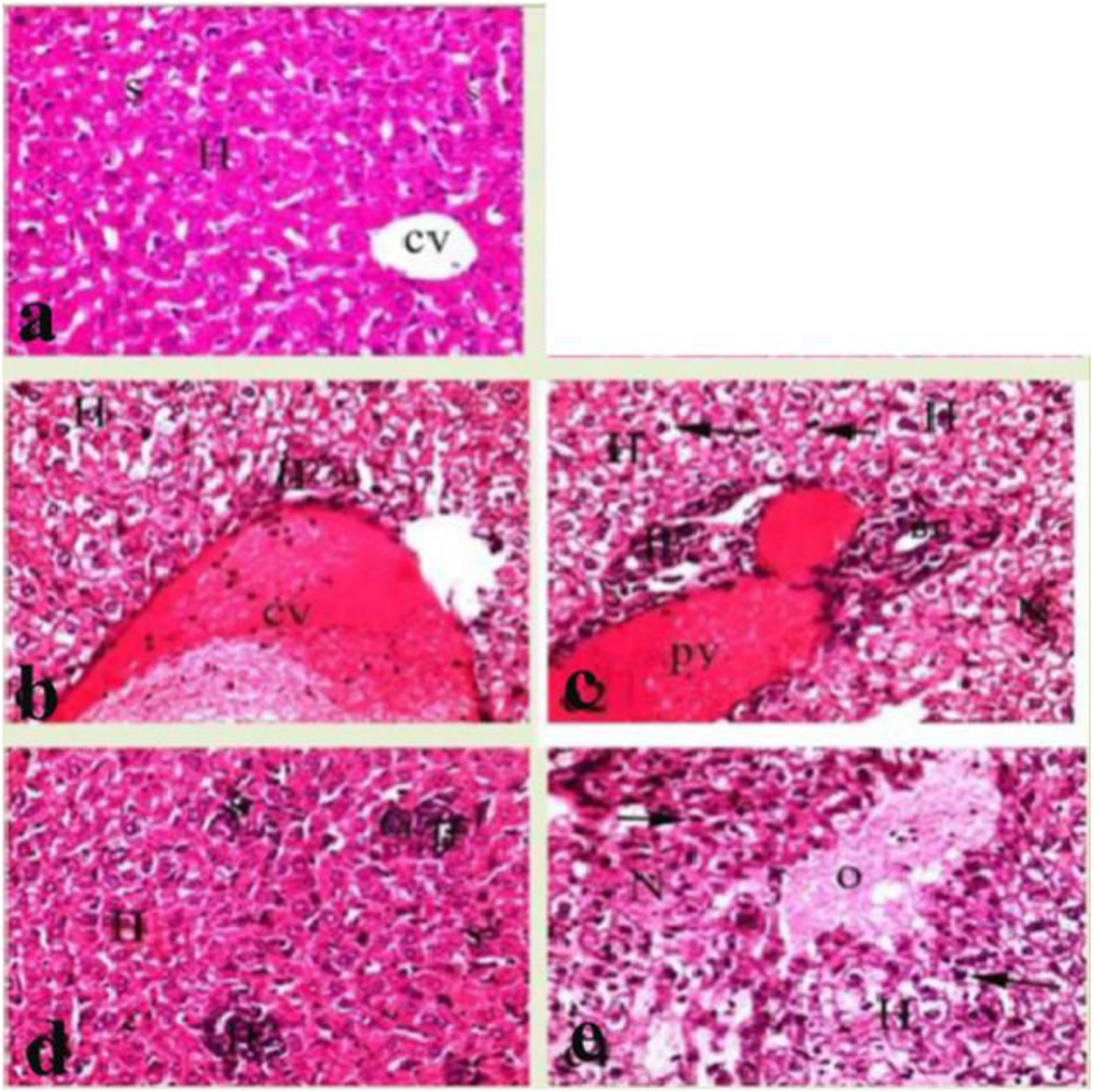

Figure 3: Light photomicrograph of liver tissues stained with H &E, X200. (a) Liver section from control animals showing normal appearing of hepatocyte (H) that radiated from central vein (CV) and separated by sinusoids (s).; **(b)** Liver section from glutamate treated group showing severe vacuolar degenerative hepatocyte (H), marked dilated congested central vein(CV) with perivascular mild aggregation inflammatory cells (IF).; (c) Liver section from glutamate treated group showing extensive vacuolar degenerative hepatocyte (H) with pyknotic nuclei (arrow), severe dilated, congested portal veins (PV) and moderate dilated bile ducts(BD) with dense aggregation of inf lammatory cells in perivascular (IF) and necrotic area (N).; (d) Liver section from glutamate treated group showing scattered dense inflammatory cells aggregation in hepatic tissues (IF) and in sinuso ids (s) with occasionally giant cells (G) .; **(e**) Liver section from glutamate treated group showing necrotic areas (N), edema (O) and marked vacuolar degenerative hepatocyte (H) with pyknotic nuclei (arrow).

Kidney tissue

Microscopically examination of kidney sections from mice revealed normal structure with normal glomeruli, Bowman's space and renal tubules (Figure 4a). On another hand, treatment animals with MOGL resulted in destruction normal structure of kidney tissues as evidence by atrophied vacuolated glomerular tuft, narrow Bowman's space and edema. Most renal tubules showed hyaline casts in their lumen and others showed severe degenerative change in their epithelial cell lining with pyknotic nuclei (Figure 4b). Some areas, revealed segmentation of most glomerular tuft, swelling of other tuft combined with congested dilated blood vessels with thickened wall, interstitial hemorrhage and scattered aggregation of inflammatory cells (Figure 4c).

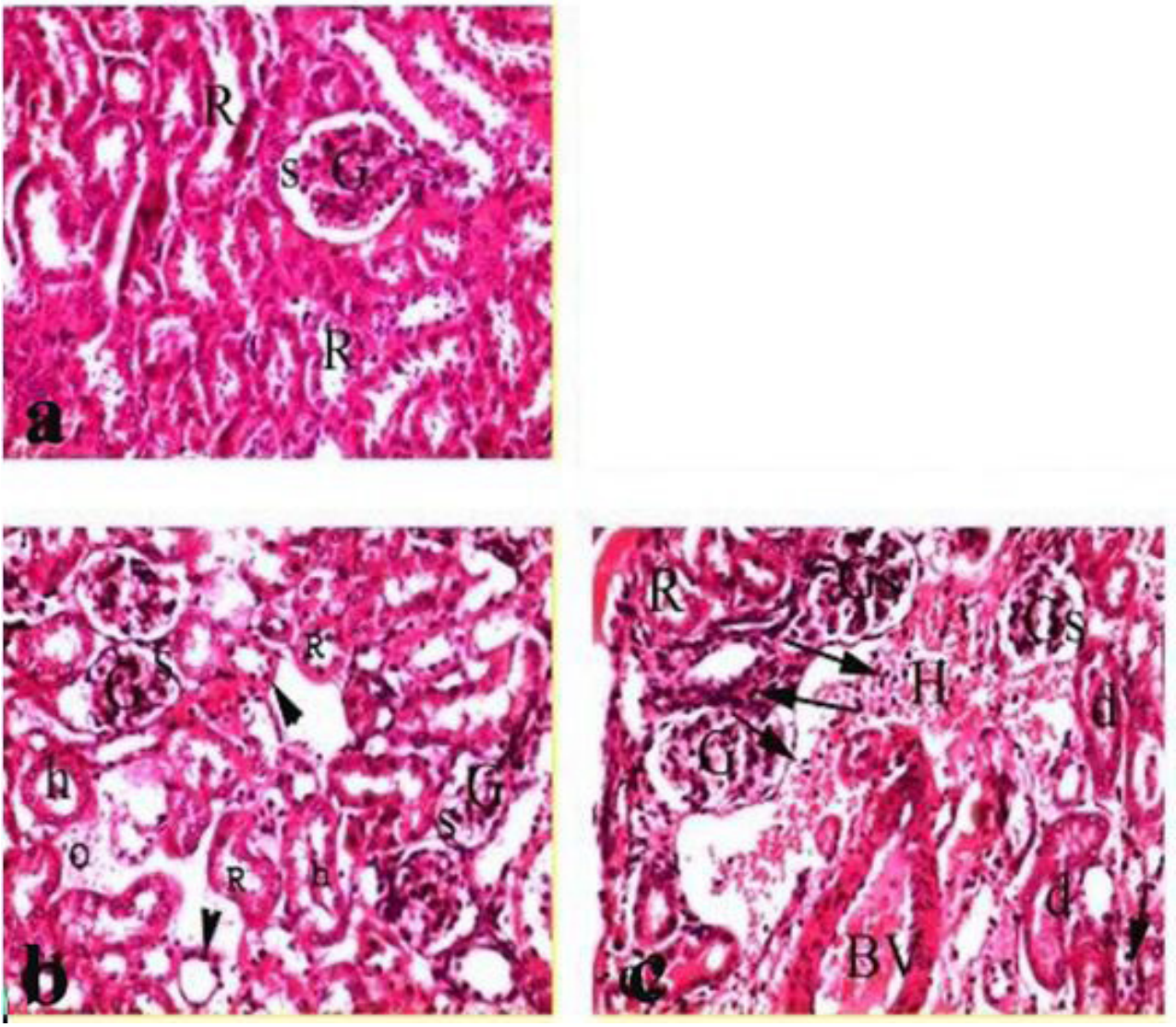

Figure 4: Light photomicrograph of kidney tissues stained with H &E, X200. (a) Kidney section from control animals showing normal glomeruli (G), Bowman's space (S) and renal tubules (R).; (b) Kidney section from glutamate treated group showing atrophied vacuolated glomerular tuft (G), narrow Bowman's space(S) and edema (O). Most renal tubules (R) showed hyaline casts (h) in their lumen and others showed severe degenerative change in their epithelial cell lining with pyknotic nuclei (arrow).; (C) Kidney section from glutamate treated group showing lobulated glomerular tuft (Gs), swelling vacuolated glomerular tuft (G), desquamating in lumen of some renal tubules (d). thickened wall of congested dilated blood vessels (BV), interstitial hemorrhage (H) and scattered aggregation of inflammatory cells infiltrations (arrow).

Fulgent stain for detect DNA content

DNA content was demonstrated as a magenta color in sections staining with fulgent reaction. Heart, spleen, liver and kidney sections from control animals revealed normal DNA contents (Figure 5a). However, animals treated with monosodium glutamate showed condensed DNA in pyknotic nuclei of cardyomyocyte, cells of spleen, hepatocyte in liver tissues, and epithelial lining cells of renal tubules in kidney tissues (Figure 5c).

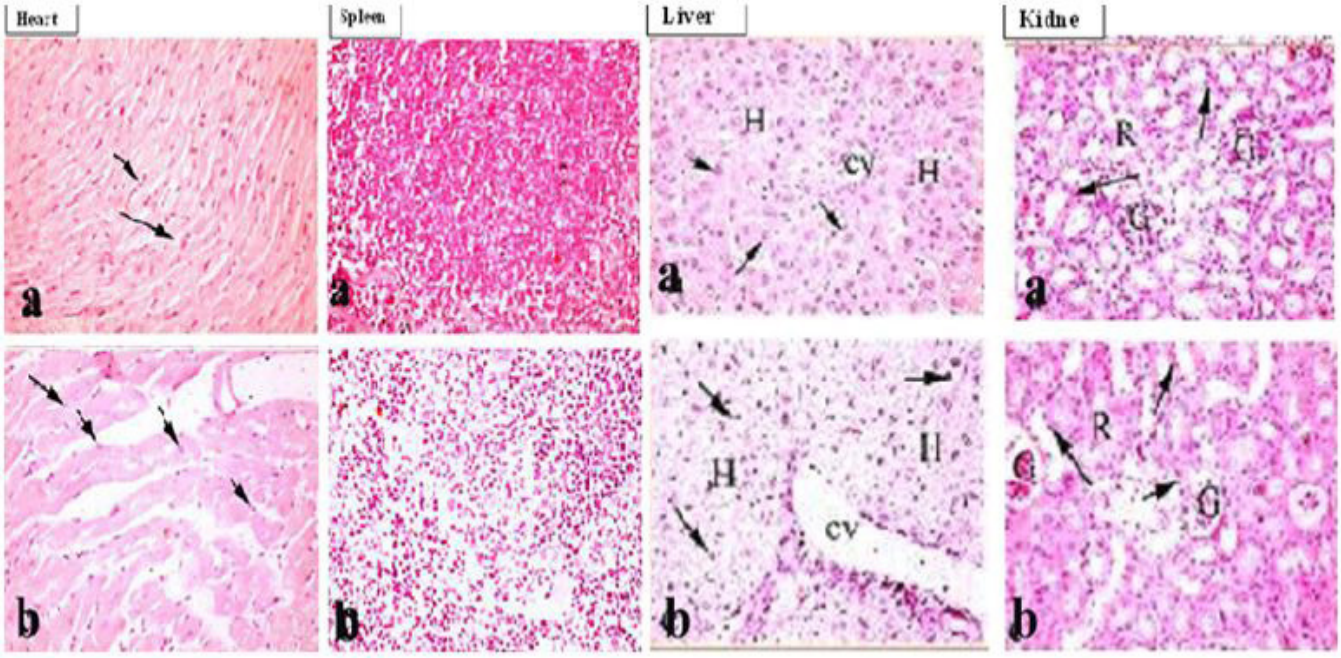

Figure 5: Sections from heart, spleen, liver and kidney stained with Fulgent, X200
from: (a)control mouse showing normal content of DNA; (c) Glutamate treated group showing decline in content of DNA.

Immunohistochemical analysis (Nuclear factor κB)

Immunohistochemistry staining showed increase in the level of NF κB in heart, spleen, liver and kidney tissues of animals treated with monosodium glutamate **(Figure 6.c)** compared to control group (Figure 6a).

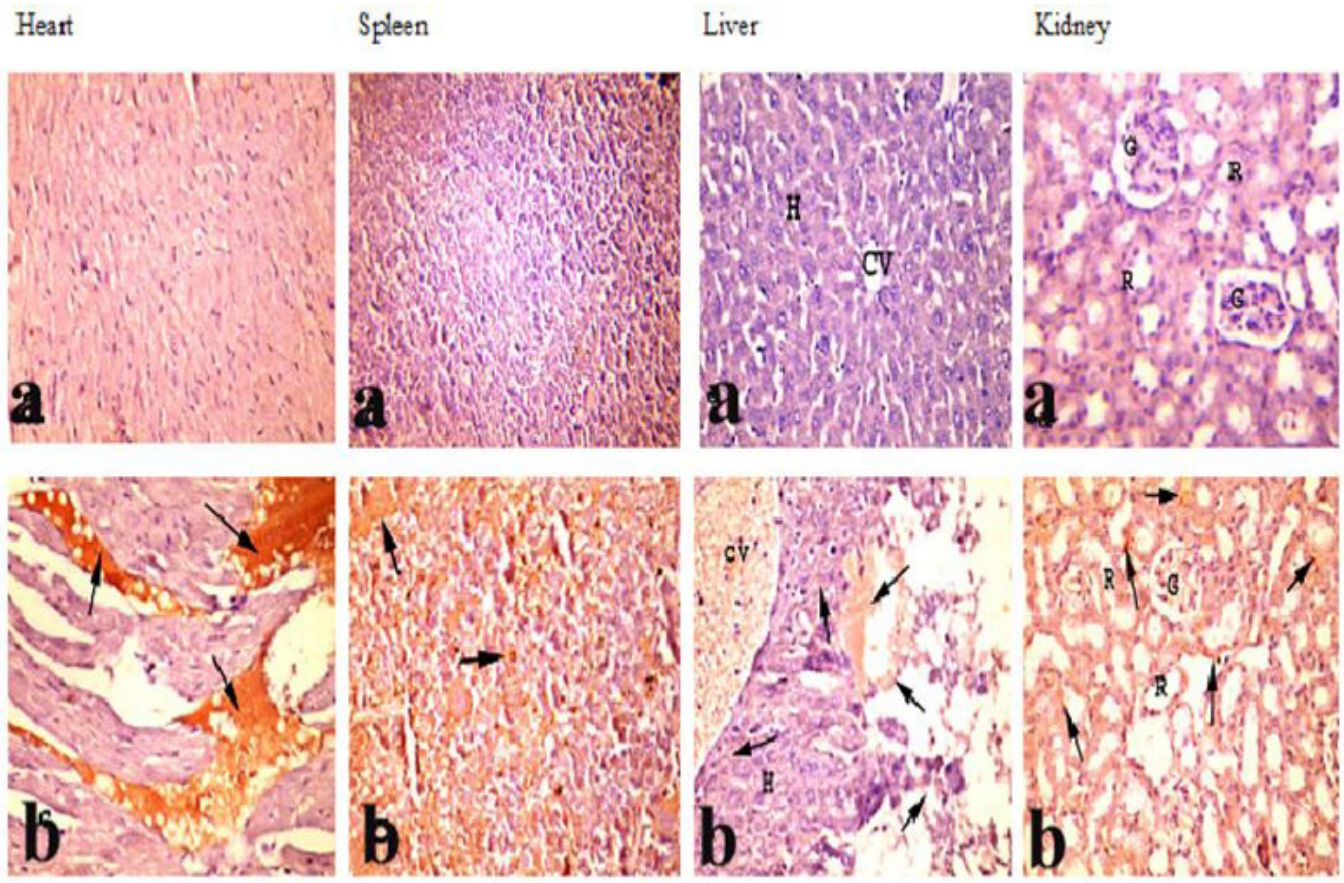

Figure 6: A Sections from heart, spleen, liver and kidney stained with Immunohistochemistry staining of NF κB, X200: (a) control mouse showing noexpression of NF-kB; (c) glutamate treated group showing significant increase in NF-kB.

	Level of *NF κB* Heart (Mm2) (Mean ± S.D.)	Level of *NF κB* spleen (Mm2) (Mean ± S.D.)	Level of *NF κB* liver(Mm2) (Mean ± S.D.)	Level of *NF κB* kidney (Mm2) (Mean ± S.D.)
Control group	**0±0**	**0±0**	**0±0**	0±0
Glutamate treated group	**129±9.16***	**173.2±35.5***	**93.3±10***	**67±13***

Ten animals were used in each group. Data are represented as mean ± SD

*P < 0.01 is highly significant

Table 1: Effect of monosodium glutamate on areas % of NF κB in heart, spleen, liver and kidney tissue

Discussion

Current study aimed to evaluate the effect of common uses of monosodium glutamate on heart, spleen, liver and kidney of male Swiss albino mice using histological, histochemical, and immunohistochemistry examinations studies. We reported that common oral administration of monosodium glutamate resulted in histological alterations, lower DNA content and increase activity of NF κB, in all examined tissues, these were in agreement with [20, 17, 28]. These observed histological alterations in all examined tissues of animals treated with monosodium glutamate could be attributed to the presence receptors of glutamate on tissues. Glutamate is considered as the predominant excitatory neurotransmitters in in peripheral neural and non-neural tissues [29]. Likewise, [30, 31, 32] stated that glutamate receptors have important role in the pathophysiology of different organ systems and pathophysiology of syndromes and diseases such as epilepsy, stroke, schizophrenia, addiction, depression, anxiety, Alzheimer's, Huntington's, Parkinson's, brain injury and heart diseases.

Another reason for tissues damage observed in the present study could be attributed to elevation of free radical species, oxidative stress, lipid peroxidation, malondialdhyde levels and to reduction antioxidant enzymes as superoxide dismutase, catalase, glutathione peroxidase activities [21, 14, 22, 33, 34]. It is well known that oxidative stress leads to activation of nuclear factor-jB (NF-jB) signaling pathway which is crucial for regulation of many genes involved in inflammatory responses, as tumour necrosis factor-a (TNF-a), inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and caspase family of proteases leading eventually to cell death [35, 36]. Our result supported by work done by [37, 22] who found that administration monosodium glutamate resulted in increased superoxide radical production and other reactive oxygen species thereby induce oxidative stress in the hepatic tissues, [38, 22]. Increase levels of triglycerides, Low density lipoprotein-cholesterol and Volatile low density lipoprotein-cholesterol and decreasing high density lipoprotein cholesterol were proposed as the cause of coronary heart.

[22, 37] stated that elevated levels of aspartate transaminase, alanine transaminase and lactate dehydrogenase enzyme activities and lipid profile as cholesterol, triglycerides levels could be the reason of the hepatocellular damage induced by monosodium glutamate [39-41].

Conclusions

Our research indicated that cerium oxide nanoparticles has ability to inhibit most of the pathological lesions in the cardiac and splenic tissues induced by common uses of monosodium glutamate as manifested the light microscopic examination, histochemical, immunohistochemistry examinations.

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Availability of data and materials

The national organization for drug control and research provided some of materials and data.

Authors' contributions

S.R. Hamad has done all the working of the manuscript. The author read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing Interests

The author declares that he/she has no competing interests.

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