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Protective Roles of Green Extract Zinc Oxide Nanoparticles on Monosodium Glutamate-Induced Hepatotoxicity and Nephrotoxicity in Female Rats

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Abstract

Monosodium glutamate (MSG) is the sodium salt of glutamic acid, it's noxious to human and experimental animals. Nowadays, Zinc oxide nanoparticles (ZnO-NPs) are among the most widely used metal oxide nanoparticles in biological applications because of their cost-effectiveness and superior biocompatibility. Current research aims to assess ZnO-NPs protective effect against MSG-induced hepatotoxicity and nephrotoxicity in rats. In the present investigation, 16 female mature rats were randomly distributed over four groups. The rats of the first group were daily received 1 ml normal saline intraperitoneally, the rats of second group were administrated with 4 mg/kg MSG by gavage, the rats of third group were administrated with 10 mg/kg ZnO-NPs intraperitoneally, and the rats of fourth group were administrated with the mixture of the MSG/ZnO-NPs. After 14 days, all rats were weighed; then, the liver and kidneys were processed using histopathological techniques, and blood specimens were used for biochemical analysis. MSG generated various histological changes in liver tissues, including hepatocyte deterioration, inflammation, and vascular congestion.

Regarding the kidney, certain histological alterations, such as a contracted glomerulus, inflammatory infiltration, congestion, and tubule dilatation following MSG treatment, were detected. Regarding biochemical parameters, MSG elevated each AST, ALT, ALP, urea, and MDA level. More importantly, ZnO-NPs could decrease the negative influences of histological and biochemical changes that MSG causes in both the liver and kidney of rats. ZnO-NP therapy improved the aberrant histological changes in the liver and kidneys caused by MSG.

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1. Introduction

Glutamic acid is one of the naturally occurring non-essential amino acids. Monosodium glutamate (MSG) is the sodium salt of glutamic acid; it is a flavor enhancer that is frequently employed to improve the meaty flavor of food [1]. Glutamic acid is the key component of most tissues' proteins and peptides [2]. It's commercially produced and exists in many different foodstuffs, such as fish, meat, milk, chicken, cheese, and some vegetables [3]. In addition, as the most widely consumed food, the brand name of MSG is Ajinomoto, or Chinese salt, which is frequently added to a wide variety of foods, including pasta, potato chips, a variety of snacks, soups, and sauces in cans, marinated meats, frozen meals, and roasted and stuffed poultry [4]. However, MSG has been identified as a key contributor to the development of health problems, including obesity, metabolic disorders, and Chinese restaurant syndrome [5]. In addition, oxidation stress induced by MSG leads to damage in different parts of the body, such as the eyes [6], liver, kidney, brain, testis [7] and epididymis [8]. Free radicals are produced as part of the MSG damage pathway, which modifies genomic information and mitochondrial activity [9]. Histological analysis revealed liver parenchymal metastases [10].

Zinc oxide (ZnO) is among the highly promising inorganic oxides that have recently attracted many scientists' interest in nanoparticle biosynthesis because of its unique properties and numerous uses in photocatalytic degradation, solar cells, and drug delivery [11]. One of the biosynthesized nanoparticles of ZnO is ZnO-NPs, which are used in beauty items and sunblock as they have strong UV immersion properties [12]. ZnO-NPs are an inexpensive, not as hazardous, substance with remarkable medicinal properties, including anti-inflammatory, antibacterial, anti-diabetic, drug discovery, wound healing, and bioimaging [13, 14]. Moreover, ZnO-NPs have biomedical applications that involve antioxidants and anticancer [15]. ZnO-NPs have renoprotective properties against acute renal injury [16] and chronic renal syndrome [17] in rats. The current investigation aimed to elucidate how ZnO-NP administration's antioxidant activities mitigated the hepatotoxicity and nephrotoxicity caused by MSG in rats.

2. Materials and methods

2.1. Experimental animals and design

The present investigation employed 16 mature female albino rats (8-10 weeks old), weighing between 200 and 220g and in good health. The rats were distributed unsystematically into 4 groups (4 rats/group). Group one was the control, where rats received normal saline by intraperitoneal injection daily. Group two rats were received intraperitoneally 4 mg/kg of MSG daily. Group three rats received 10 mg/kg ZnO-NPs by gavage daily. Group four rats received MSG in a dose of 4mg/kg intraperitoneal injection and 10 mg/kg ZnO-NPs by gavage daily. The experiment lasted 14 days, and all rats received normal nourishment and tap water *ad libitum.* The Animal Ethics Committee of the College of Science, Salahaddin University, approved this work (Code: 45/204). The laboratory for advanced histology in The Department of Biology, College of Science, Salahaddin University, served as the site of this study's experimental work.

2.2. Monosodium glutamate (MSG) dose preparation

Powdered MSG was purchased from the local market in Erbil, Kurdistan region, Iraq. It was prepared in normal saline with a 4 mg/kg body weight concentration.

2.3. Zinc oxide nanoparticles (ZnO-NPs) dose preparation

A zinc oxide nanoparticle was prepared by A Barzinjy [18] at Soran University, Soran, Iraq. Sonication was used to prepare a stock suspension (10 mg\mL) of ZnO-NPs in normal saline for 30 seconds in an ultrasonic homogenizer. The particle suspensions were placed on ice for 15 seconds and sonicated for 2.5 minutes at a power of 400 W on ice. Then, the ZnO-NPs were vibrated for 2 minutes immediately before the eventual injection. The concentration of 10 mg/kg body weight was made from this stock suspension in normal saline.

2.4. Body weight recording

Every group's rat's body weight (B.W.) was recorded two times, before and after treatment. From there, the body weight gain (in grams) was computed as follows: body weight, body weight after treatment, and body weight before treatment.

2.5. Anesthesia, dissecting and remove organs

After 14 days of exposing rats, they were anesthetized with an intraperitoneal injection of xylazine 12mg/kg (Interchem, Halland) and ketamine hydrochloride 80 mg/kg (Trittau, Germany). After anesthetization, rats were dissected; their liver and kidneys were isolated and placed in buffered formalin 10% fixative.

2.6. Histological preparation:

The liver and kidneys of the anesthetized rats were removed, cleaned, and cut into small pieces for easy fixative penetration. They were directly fixed in 10% of the formalin buffer for at least 24 hours and then processed according to the paraffin method. The fixed pieces of liver and kidneys were dehydrated by using ethanol from low to high concentrations (50%, 70%, 80%, 95%, 100% and 100%). Then, they cleared in xylene, and an infiltration and embedding process was performed using paraffin wax. To make slides for samples, paraffin blocks were cut into 4-6 μm thicknesses of the specimen sections were made by using a rotary microtome (bright, MIC), and then slides were stained with haematoxylin (H) and eosin (E) [19, 20]. The stained slides of liver and kidney sections were examined and shot using digital light microscope (digital binocular compound microscope 40x2000x, built-in 3MP USB camera).

2.7. Biochemical analysis

2.7.1. Liver Function Tests

Serum alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin were measured using a fully automated biochemistry analyzer (Liason xl manufactured by Diasorin). The results were expressed by (U/L).

2.7.2. Renal Function Tests

Serum creatinine, uric acid, and urea were estimated using a fully automated biochemistry analyzer (Liason xl manufactured by Diasorin). The results were expressed by mg/dl.

2.7.3. Determination of Serum Malondialdehyde (MDA)

The level of serum MDA was determined spectrophotometrically with a thiobarbituric acid (TBA) solution. 50µl of the serum samples were added to 1ml trichloroacetic acid (TCA 17%). And 1 ml of thiobarbituric acid (TBA), mixed well by vortex, was incubated in boiling water for 45 minutes and then allowed to cool. One ml of TCA 70% was added, and the mixture was left to stand at room temperature for minutes, centrifuged at 2000 rpm for 15 minutes, and the supernatant was taken out for scanning spectrophotometrically 532nm [21].

2.7. Statistical analysis

GraphPad Prism version 9.0 was utilized to accomplish statistical evaluation. One-way ANOVA with Tukey's test was executed to estimate the statistically significant group variations. The data were expressed as means ± standard error (M ± SE). A p-value of 0.05 or below was measured as statistically significant [22].

3. Results and Discussion

3.1. Body weight gain

In the current research study, the body weight gain of rats receiving MSG was increased statistically ($P<0.01$) as opposed to the control group of rats. Whereas rats who received ZnO-NPs alone and in combination with MSG displayed a decrease in body weight gain but were not significantly different from those who received MSG (Fig. 1). Parallel outcomes were noticed by Muslim [23]. *He, et al.* [24] displayed that the MSG intake was related with the body weight. In addition, Mohammed, *et al.* [1] showed that MSG prompted a significant elevation in ending mass of the body and weight gain in rats.

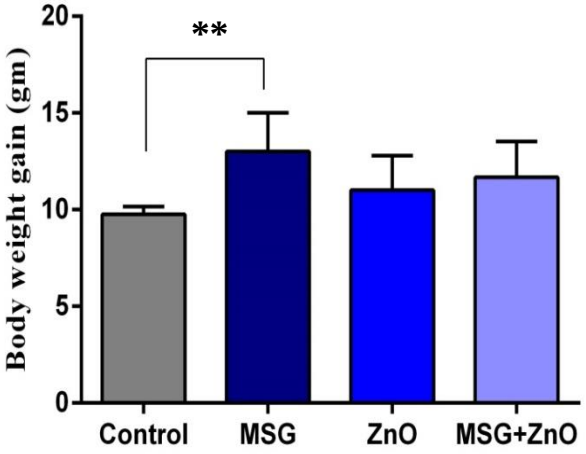

Figure 1: The body weight gain in rats received MSG, ZnO-NPs and MSG/ZnO-NPs.
** = $P<0.01$

3.2. Histological analysis of the liver

Within the ongoing study, histological analysis displayed alterations in the liver, including congestion of blood vessels with blood cells, hepatic cell degeneration, fatty changes in the hepatocytes, and inflammation of infiltration along the portal vein due to receiving MSG, which they were not clearly observed in rats of the control group (Fig. 2 and 3). MSG might be harmful to the liver from many different points of view, as studies have shown the poisonous properties of MSG on humans [25] and animal tissues [4, 26]. Hazar [27] showed that oxidative stress is crucial in liver deterioration and fibrosis progress. MSG might be the main cause of many inflammatory diseases; this decision comes from the occurrence of inflammation in the liver tissues of rats that received MSG. The inflammatory markers, including TNF-α and IL-6, were superfast in concentration, and MSG could induce oxidative stress by creating free radicals, including oxygen radicals and hydrogen peroxide, which are known to cause damage in DNA and cell membrane peroxidation that finally lead to cell death [28, 29]. In addition, oxidative stress was noticed in rats' livers when administrated with MSG orally [25]. In addition, in the present research, treated with ZnO-NPs extract, the architecture of the liver in rats was protected, either alone or in combination with MSG (Fig. 4 and 5). These results confirm the hepatoprotective property of ZnO-NPs and align with other research studies, which showed that the ZnO-NPs utilized a partial hepatoprotective outcome against MSG [9]. *Abbas, et al.* [30] Reported that the plant extract ZnO-NPs exhibit hepatoprotective impact.

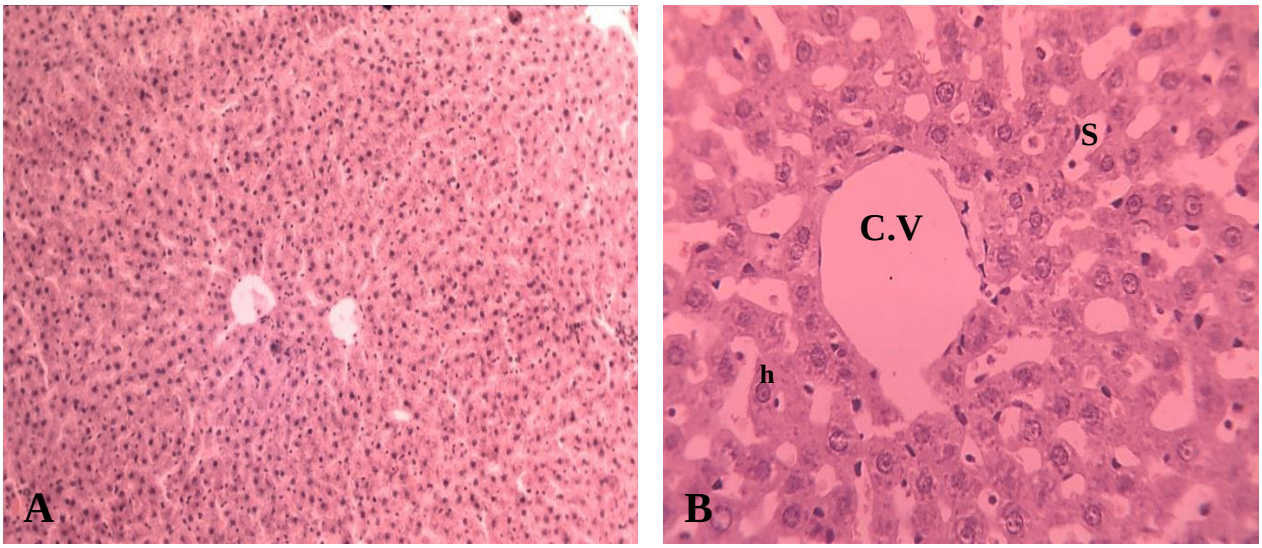

Figure 2: Histological liver section of rats of the control group. C.V: central vein, S: sinusoids, h: hepatocytes, H&E.(A):100X,(B):400X.

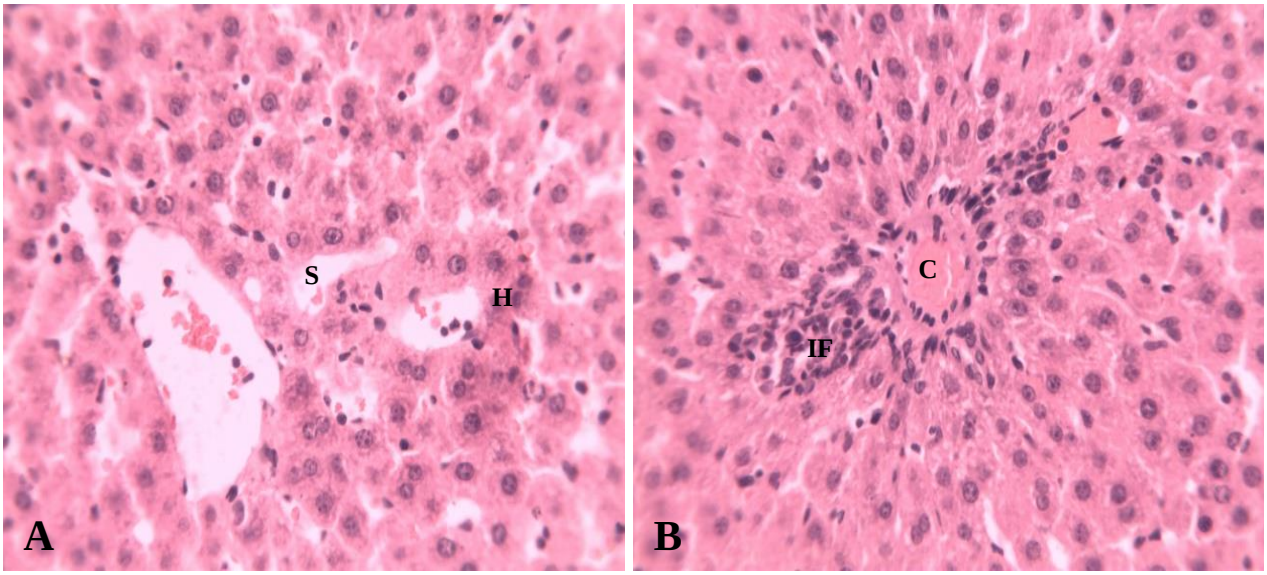

Figure 3: The histological section of the liver of rats treated with MSG. A) Liver cell degeneration (H) and dilation in blood sinusoids (S). B) Inflammatory infiltrated (IF) close to the portal vein and the vein seen congested with blood cells (C)., H&E. Both are 400X.

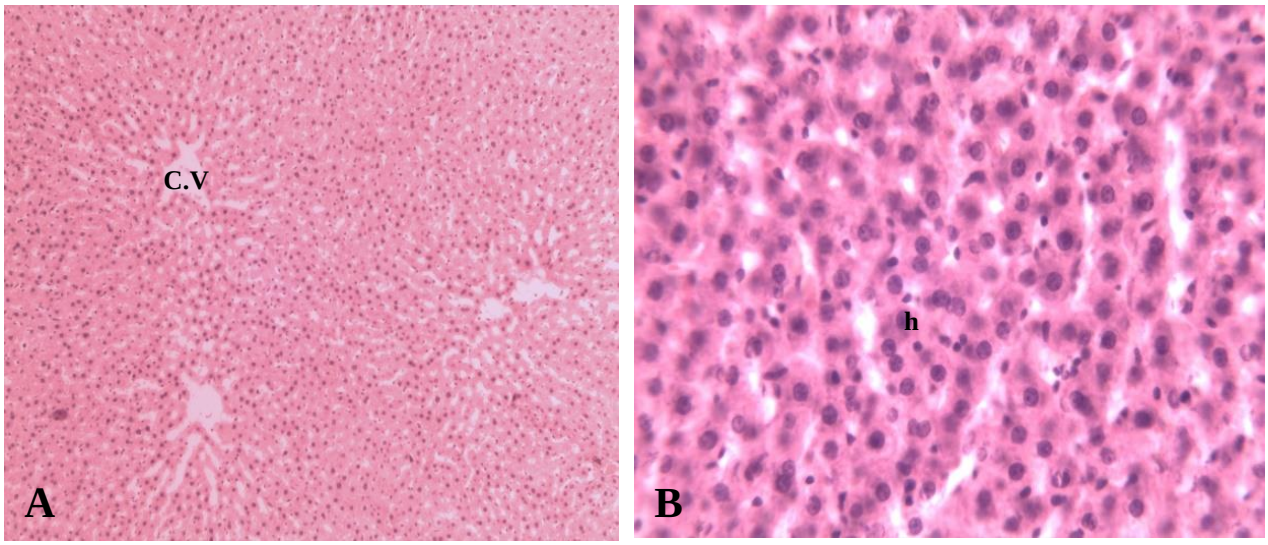

Figure 4: Histological photomicrograph of the liver of rats treated with ZnO-NPs. C.V: central vein, h: hepatocytes, H&E.(A):100X,(B):400X.

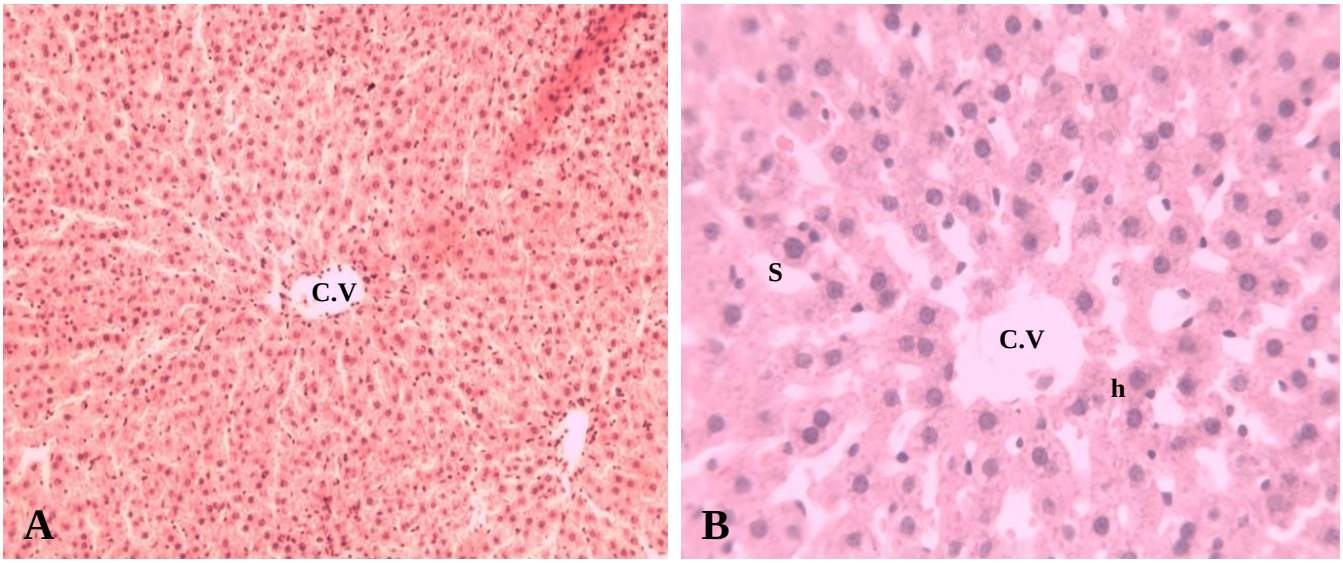

Figure 5: Histological photomicrographs of the liver of rats treated with MSG/ZnO-NPs. C.V: central vein, h: hepatocytes, S: sinusoid H&E.(A):100X,(B):400X.

3.3. Biochemical Study of the Liver Functions

Biochemically, MSG-affected liver function tests reflected by the statistically significant increase of serum alanine aminotransferase (ALT) when compared to the ZnO-NPs and MSG/ZnO-NPs groups, but aspartate aminotransferase (AST) and alkaline phosphatase (ALP) levels non-significant increase in comparison to the control, ZnO-NPs and MSG/ZnO NPs groups. These changes in liver function tests may be due to the mode of cell death induced by MSG. On the other hand, ZnO-NPs have a positive, beneficial effect in protecting the rat tissues and facilitating the liver function test by decreasing the level of AST, ALT, and ALP compared to the MSG group (Table 1).

The result seemingly agrees with the study of Manal Said and Nawal [31], which found that MSG administration caused significantly elevated levels of ALT serum. Akanya, *et al.* [32] reported that the ALP and ALT levels were increased with MSG administration. ZnO-NPs positively impacted ALT, AST, and ALP enzyme activities, indicating strong evidence of the protective [30]. Another study found a significant positive association between dietary ZnO-NPs concentrations and their serum ALT and AST values in rat, which means ZnO-NPs have antioxidant effects [33].

Table 1 Comparison of liver enzymes and bilirubin levels among experimental groups

Groups / Parameters	Control	MSG	ZnO-NPs	MSG/ZnO-NPs	Summary
AST	130.1±6.39	153±2.83	127.6±3.49	141.9±17.61	ns
ALT	41.83±2.88	52.33±2.93^{a}	37.97±2.73^{b}	33.3±2.96^{bc}	s
ALP	134.8±20.09	179.8±28.77	160.7±31.97	171.3±7.54	ns

Data represented by mean ± standard error. Different letters indicate a statistically significant difference between groups. MSG, monosodium glutamate; ZnO-NPs, zinc oxide nanoparticles; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; TSB, total serum bilirubin; s, significant; ns, non-significant.

3.4. Histological analysis of the kidney

Rats in the control group had kidneys with normal histological architecture, such as a normal appearance of glomeruli and kidney tubules (Fig. 6). The histological examination of the rat's kidney tissues treated with green extract Zn-NPs also showed normal renal structure with mid leukocytic cells infiltration (Fig. 7). However, as shown in figures (8 & 9), in MSG rat treated group, the kidneys revealed various histological alterations such as appearance of inflammatory infiltration leucocytes area, atrophy, shrunken tuft of glomerulus and congestion of some blood vessels when compared with the control, ZnO-NPs and ZnO-NPs/MSG groups. In addition, other morphological changes, including the dilatation of tubules, were observed. Moreover, ZnO-NPs in the ZnO-NPs/MSG treated group ameliorated the preceding histological results induced by MSG (Fig. 10). MSG caused impairment of renal structure. However, its antioxidative character protects ZnO-NPs in contrast to MSG-induced nephrotoxicity. The chronic intake of dietary MSG causes obstructive nephropathy, and MSG supplementation by oral intake induces kidney damage in adult rats [34]. MSG showed different histopathological alterations in the renal cortex with distortion of renal architecture in the form of contracted glomerular tufts, tubular dilatation, and interstitial hemorrhage, which is in agreement with remarks made by Dixit, *et al.* [35]. In addition, MSG exhibited disorganized renal structure, shrunken glomerular tufts with dilatation of the capsular space, congestion, and tubular dilatation [1]. In agreement with our finding, consumption of MSG has been shown to induce altered histoarchitecture increase tubule-interstitial fibrosis, glomerular hypercellularity, tubular swelling, and infiltration of inflammatory cells in rat kidneys [36]. Distortion of the renal cortical structures and some degree of cellular necrosis, with degenerative, atrophic, and Bowman's spaces that were sparsely distributed, were confirmed after daily administration of MSG [37]. Regarding the ZnO-NPs' influences, green extract ZnO-NPs have anti-inflammatory and anti-fibrotic properties and antioxidant actions. They can be used to treat chronic kidney disease in rats. Furthermore, ZnO-NPs decreased the impact of MSG meaningfully by reducing the level of peroxidation and improvement intracellular antioxidant in the kidneys of rats [38].

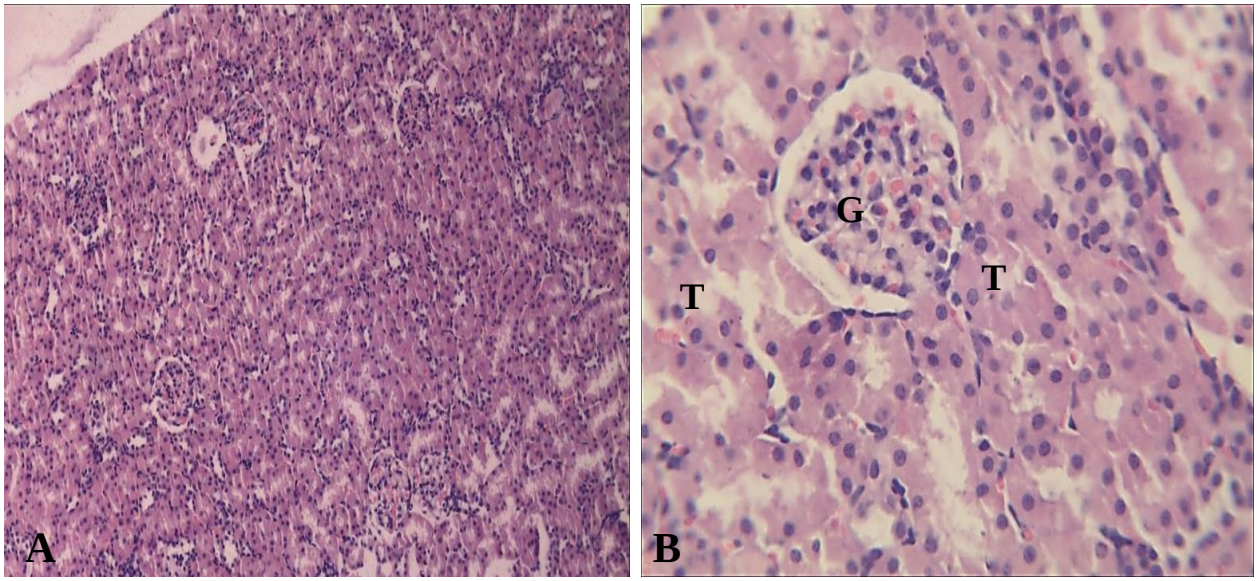

Figure 6: Photomicrographs of the kidney section from control rats illustrate healthy glomerulus (G) and kidney tubules (T), H&E. A) 100X. B) 400X.

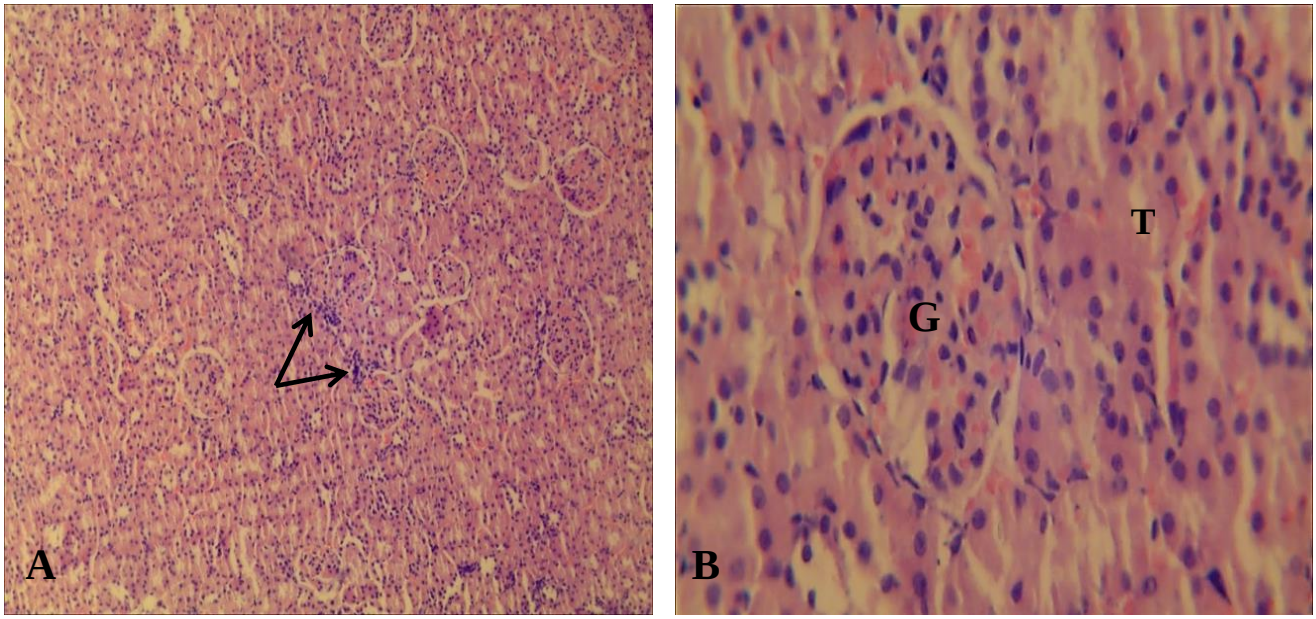

Figure 7: Paraffin sections of kidney rats of the ZnO-NPs group. A) Mid-leukocyte infiltration (arrow), H&E 100X. B) Kidney glomerulus (G) and kidney tubules (T), 400X.

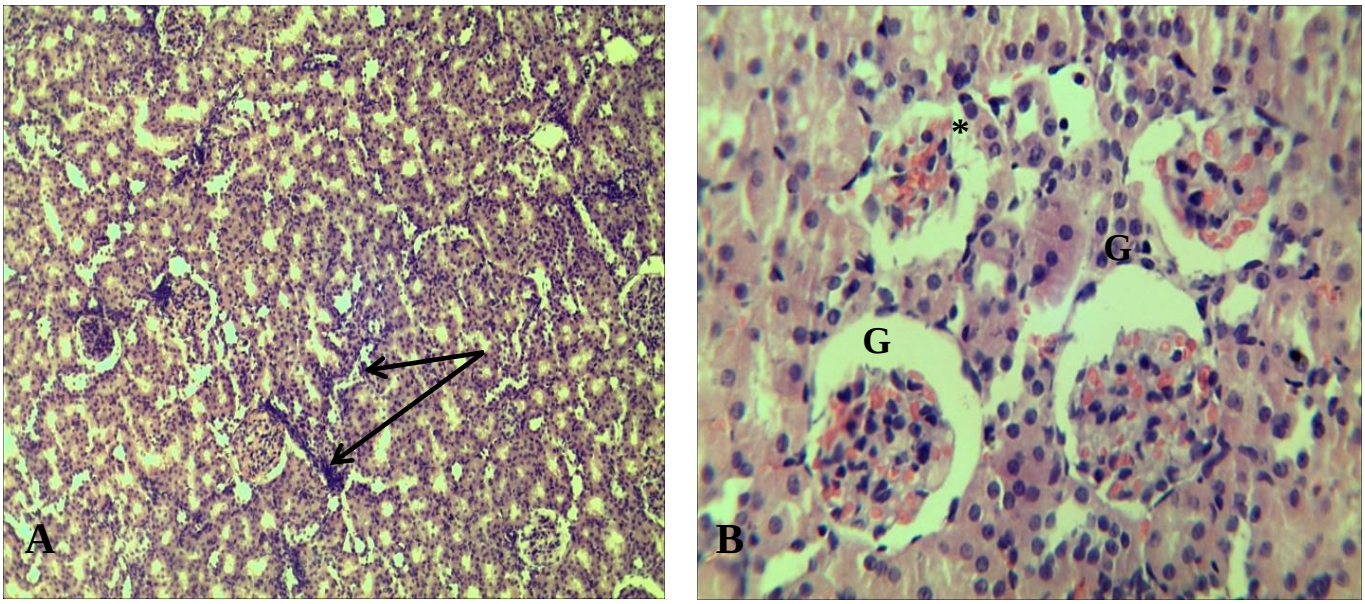

Figure 8: Photomicrographs of kidney paraffin section of MSG-treated rats. A) Inflammatory infiltration leukocytes areas (arrow), H&E, 100X. B) Shrunken tuft of the glomerulus (G) and atrophy of the glomerulus (star), H&E, 400X.

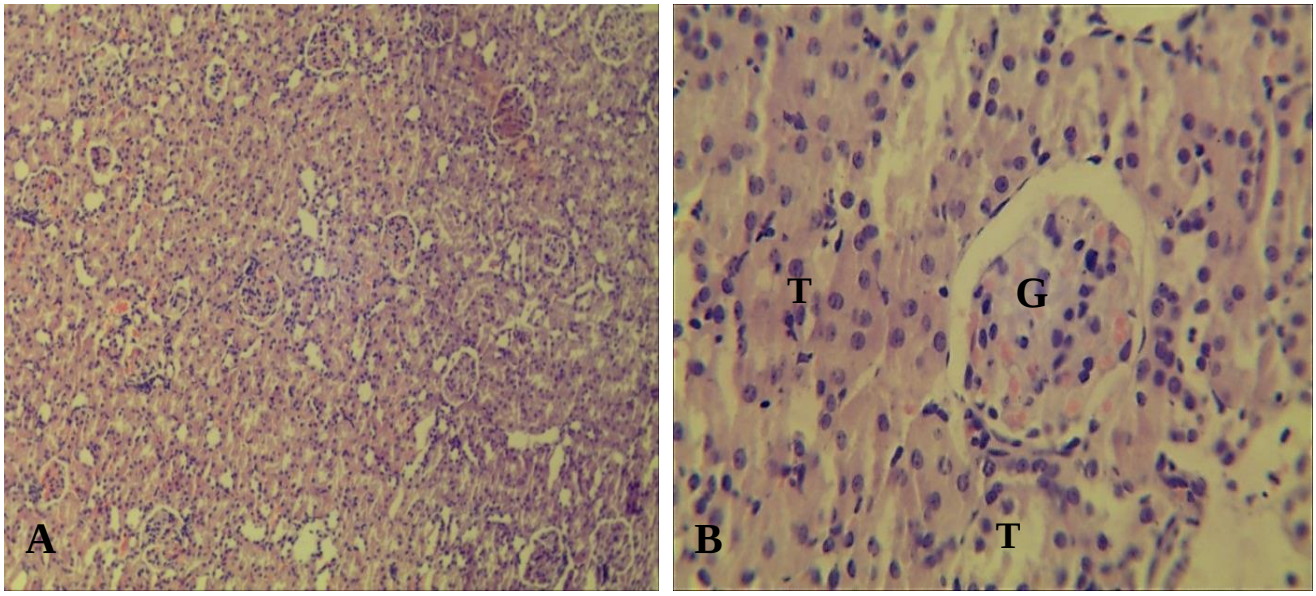

Figure 9: Photomicrographs of kidney paraffin section of MSG-treated rats. A) Congestion of blood vessels (arrow), H&E, 400X. B) Dilatation of tubules (T), H&E, 400X.

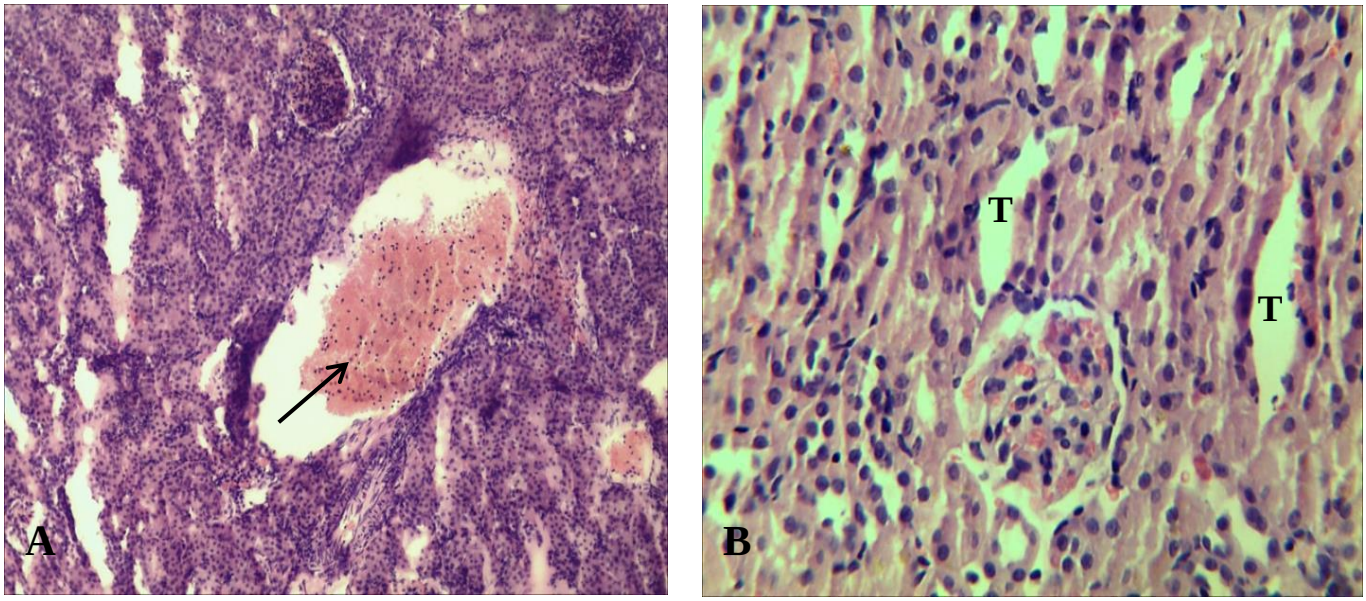

Figure 10: Photomicrographs of the kidney section from ZnO-NPs/MSG rats. A) H&E, 100X. B) kidney glomerulus (G) and tubules (T), H&E, 400X.

3.5. Biochemical study of the kidney functions

Urea and creatinine are the most common clinical markers of renal function. Table 2 demonstrated that the urea levels of MSG-treated rats are statistically significantly higher than those of control rats and statistically non-significantly elevated compared to ZnO-NPs and MSG/ZnO-NPs groups. On the other hand, daily administration of MSG at a dose of 4 mg/kg non-significantly increases creatinine levels compared to other groups. Urea is a deaminated product of protein metabolism in the liver. At the same time, creatinine is a by-product of phosphocreatine and creatine breakdown in the muscle, which is eliminated by the kidney via urine [39]. MSG administration may perturb urea metabolism in favour of increased anabolism and decreased catabolism [40]. So our findings were supported by one of the studies, which reported that renal function test (creatinine and

urea) values were increased following the administration of MSG, may be associated with kidney dysfunction [41], and using ZnONPs led to significantly reduced urea level [17].

Table 2 Comparison of renal function tests among experimental groups

Groups / Parameters	Control	MSG	ZnO-NPs	MSG/ZnO-NPs	Summary
Urea	38.95±0.53[a]	43.9±2.97[b]	40.87±0.56[b]	40.5±0.51[b]	s
Creatinine	0.32±0.04	0.38±0.03	0.36±0.01	0.34±0.02	ns

Data represented by mean ± standard error. Different letters indicate a statistically significant difference between groups. MSG, monosodium glutamate; ZnO, zinc oxide nanoparticles; s, significant; ns, non-significant.

3.6. Serum Malondialdehyde (MDA)

Daily consumption of MSG significantly increased the level of MDA when compared to control, ZnO-NPs, and MSG/ZnO-NPs groups, while green extract ZnO-NPs significantly reduced the concentration of MDA (Figure 11). MDA is among the end products of polyunsaturated fatty acid peroxidation; increased free radicals cause the overproduction of MDA, so the MDA level is shown as a marker of oxidative stress. It was found that MDA increases during the admission of MSG [42]. Exposure to MSG may elevate the MDA level, possibly due to oxidative stress induced by MSG [43, 44]. Some investigators have reported that the antioxidant and anti-inflammatory properties of ZnO-NPs might strengthen oxidative defenses by decreasing MDA concentration [17, 45].

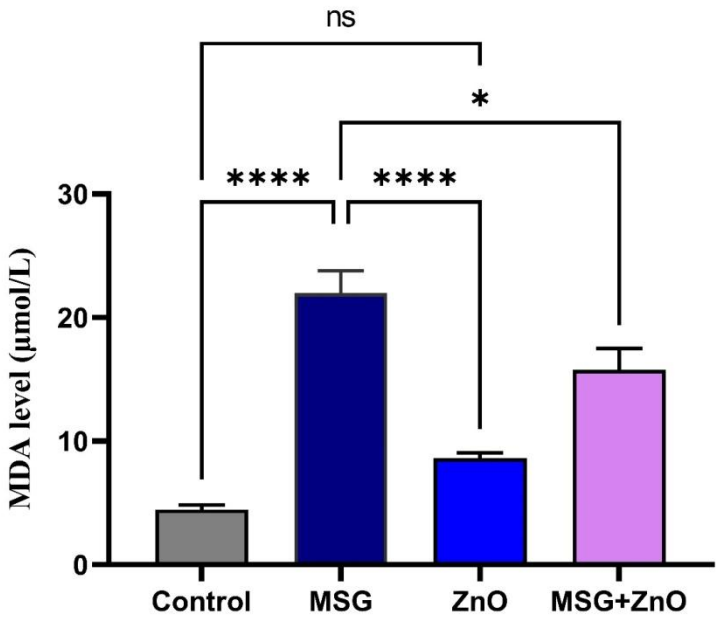

Figure 11: MDA level in serum of rats. *= p< 0.05 and ***= p< 0.001.

4. Conclusion

Administration of MSG could lead to renal and hepatic tissue damage, while green extract ZnO-NPs had a protective influence and improvement against impairment of histopathological changes.

5. Acknowledgments

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6. Declarations

There are no conflicts to declare.

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الأدوار الوقائية للمستخلص الأخضر للجسيمات النانوية من أكسيد الزنك على السمية الكبدي والكلوية الناجم عن الغلوتامات أحادية الصوديوم في إناث الجرذان

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المستخلص:
الغلوتامات أحادية الصوديوم (MSG) هو ملح الصوديوم لحمض الجلوتاميك، وهو ضار للبشر والحيوانات التجريبية. في الوقت الحاضر، تعد جسيمات أكسيد الزنك النانوية (ZnO-NPs) من بين جسيمات أكسيد المعدن النانوية الأكثر استخدامًا على نطاق واسع في التطبيقات البيولوجية بسبب فعاليتها من حيث التكلفة وتوافقها الحيوي الفائق. الغرض من البحث الحالي هو تقييم التأثير ZnO-NPs ضد التسمم الكبدي و الكلوية الناتج عن MSG لدى الجرذان. في هذا البحث، تم استخدام 16 أنثى فأر ناضجة وتم توزيعها على أربع مجموعات عشوائيا. تم إعطاء فئران المجموعة الأولى عبارة عن مجموعة سيطرة يومياً 1 مل من المحلول الملحي عن طريق الحقن ، وتم إعطاء فئران المجموعة الثانية 4 ملغم / كغم من MSG عن طريق التجريع الفمي ، وتم إعطاء فئران المجموعة الثالثة 10 ملغم / كغم من ZnO-NPs عن طريق الحقن. وتم إعطاء فئران المجموعة الرابعة خليط من MSG/ZnO-NPs . بعد 14 يوما، تم وزن جميع الفئران ومن ثم تشريحها لتحضير الكبد والكلى للفحص المجهري وعينة الدم للتحليل الكيميائي الحيوي . أنتجت MSG مجموعة من التغيرات النسيجية في أنسجة الكبد بما في ذلك تدهور خلايا الكبد، والالتهاب واحتقان الأوعية الدموية. فيما يتعلق بالكلى، تم الكشف عن بعض التغيرات النسيجية مثل تقلص الكبيبة، والارتشاح الالتهابي، والاحتقان وتوسع الأنابيب بعد علاج الغلوتامات أحادية الصوديوم فيما يتعلق بالمعايير البيوكيميائية، قامت MSG برفع مستوى كل من AST وALT وALP واليوريا وMDA. والأهم من ذلك، أن ZnO-NPs يمكن أن تقلل من التأثيرات السلبية للتغيرات النسيجية والكيميائية الحيوية التي تسببها الغلوتامات أحادية الصوديوم في الكبد والكلى لدى الفئران. أدى ZnO-NP إلى تحسين التغيرات النسيجية في الكبد والكلى الناجمة عن MSG.