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Structural Changes in Renal Cortex of Adult Male Albino Rats Treated with Monosodium Glutamate and the Alleviating Effects of Curcumin and Hesperidin: A Biochemical, Histological and Immunohistochemical Study

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ABSTRACT

Background: Monosodium glutamate (MSG) is a dietary additive that induces oxidative stress in tissues. Curcumin and hesperidin are natural compounds with multiple medicinal properties.

Objective: This study aimed to evaluate whether curcumin and hesperidin exert protective effects against MSG-induced renal injury.

Materials and methods: Fifty adult male albino rats were divided into five groups (10 each). Group I served as control, group II received MSG (4 g/kg/day orally), group III received MSG plus curcumin (150 mg/kg/day), group IV received MSG plus hesperidin (100 mg/kg/day) and group V received MSG with both curcumin and hesperidin. Treatments lasted four weeks. Kidney samples were assessed biochemically, immunohistochemically, and histologically, followed by morphometric and statistical analysis.

Results*:* MSG-treated rats showed significant increases in serum urea, creatinine, and tissue MDA, with reductions in GSH and SOD compared to controls. Histological examination revealed renal cortex impairment, glomerular atrophy, dilated capsular spaces, tubular epithelial degeneration, exfoliation, and abundant collagen fibers around glomeruli and tubules. Immunostaining demonstrated strong positive reactions for BAX and PCNA. Administration of curcumin or hesperidin alone (Groups III and IV) resulted in moderate biochemical and histological improvement. However, combined treatment (Group V) markedly ameliorated renal damage, restoring tissue structure and reducing oxidative and apoptotic markers more effectively than either agent alone.

Conclusion: Curcumin and hesperidin provide protective effects against MSG-induced renal damage, with combined administration offering superior preservation of kidney tissue integrity and function.

Keywords: Monosodium glutamate, Curcumin, Hesperidin, Renal cortex.

INTRODUCTION

Monosodium glutamate (MSG) is commonly incorporated into canned vegetables, prepared meat, soups and oriental cuisine because of its ability to improve flavor. The "Umami" taste perception can be evoked by this chemical via the same sensory molecular pathways [1].

The sodium salt of glutamic acid makes up this diet additive, which is used to enhance flavor and taste. It is commonly known that eating MSG raises the reactive oxygen species (ROS), that can lead to DNA, lipids, and proteins being damaged by free radicals. Lipid peroxidation results from damage of cell membrane's polyunsaturated fatty acids. These factors all contribute to apoptosis, which results in cell death. After being broken down by the liver, these radicals are eliminated by the kidneys. Consequently, it became evident that prolonged MSG consumption was detrimental to the kidneys [2].

Curcumin is shown to provide a wide range of beneficial benefits, comprising anti-inflammatory, antioxidant, anticarcinogenic, antigenotoxic, anticoagulant, and anti-contagious qualities [3]. Curcumin therapy improved kidney function and reduced glomerulonephritis-related inflammation and fibrosis in mice [4].

Citrus fruits, such as lemons, sweet oranges, bitter oranges, and satsuma mandarins, can yield large amounts of hesperidin (HS), a flavanone glycoside. It has anti-inflammatory, anti-allergic, anticarcinogenic, hypolipidemic, and vasoprotective qualities [5]. One of hesperidin's main functions is to scavenge radicals, which returns the redox profile of treated cells to normal. In cells treated with HS, the antioxidant system was boosted and reactive oxygen species (ROS) were decreased [6].

Therefore, this study aimed to determine if monosodium glutamate could affect adult male albino rats' kidney and if curcumin and hesperidin could have a protective value.

MATERIALS AND METHODS

Materials

Animals: Fifty healthy adult male albino rats weighing 200–250 grams were acquired from the Faculty of Veterinary Medicine at Benha University. The rats were given a standard nutrition and housed in cages at a consistent temperature of 25 °C. Following the "Guide for the Care and Use of Laboratory Animals" the experiment was carried out. This experiment was conducted in Anatomy Department, Benha Faculty of Medicine in the period from October 2024 to November 2024.

Chemicals:

Monosodium glutamate: MSG (Chinese salt) was acquired from Sigma-Aldrich company as a white crystalline granule, purity ≥ 99% ($C_5H_8NNaO_4$)

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(Figure 1). We dissolved it in distilled water to produce the required dosage.

Curcumin powder: Purity ≥ 65% of ($C_{21}H_{20}O_6$) bright yellow to orange color powder, obtained from Sigma-Aldrich Company in the USA (St. Louis, MA, USA) we dissolved it in corn oil.

Hesperidin (HSD): Hesperidin (powder of purity ≥ 97.0%, CAS No: 520-26-3) was acquired from the manufacturing company Sigma Aldrich Corporation (St. Louis, MA, USA). Hesperidin was given orally by gastric gavage after being dissolved in corn oil.

Figure (1): Monosodium Glutamate (Chinese salt).

Experimental design: The fifty rats were divided into five equivalent groups (I, II, III, IV and V) after a one-week acclimatization period.

Group I (Control group): Ten rats separated into two subcategories (5 animals in each):
Subgroup (IA): (Negative control): the rats were fed on essential diet and purified water for 4 weeks.
Subgroup (IB): (Positive control): the rats were given corn oil orally (2 ml/kg /day) via gastric tube once daily for 4 weeks.

Group II (MSG treated group): For four weeks, ten rats were administered 4 gm/kg/day of MSG via a gastric tube once daily dissolved in distilled water and taken orally [7].

Group III (MSG + Curcumin treated group): For four weeks, ten rats each received 150 mg/kg body weight/day of curcumin melted in corn oil in addition to MSG, as in group II via gastric tube once daily for four weeks [8] .

Group IV: (MSG + Hesperidin treated group): Ten rats each were administrated MSG, as in group II in addition to 100 mg/kg hesperidin via a gastric tube, melted in corn oil once daily for four weeks [9].

Group V: (MSG + Curcumin+ Hesperidin treated group): Ten rats each were given 150 gm/kg curcumin and 100 mg/kg hesperidin in addition to MSG, as in group II. via a stomach tube once a day for four weeks.

Sample collection: just before the experiment termination, using capillary tubes, blood samples were drawn from the tail vein and put into Eppendorf tubes with heparin (20 ml, 200 IU/ml) for chemical analysis. Sodium thiopental (40 mg/kg) was intraperitoneally injected to euthanized the animals 24 hours after the last dose rendering to the strategies of Ethics Committee of Medical Research of Faculty of Medicine, Benha University [10]. A mid-ventral incision was performed down the full length of the abdominal cavity in each rat to expose the abdominal wall, and the kidney was obtained. For light microscopy, specimens primarily from the kidney section were acquired and prepared.

Biochemical analysis:
Determination of kidney functions: Utilizing the traditional colorimetric method, the serum urea and creatinine levels were estimated using the Quanti Chrom TM Assay Kits (DIUR-500 and DICT-500), which are based on the improved Jung and Jaffe techniques, respectively [11].

Determination of the oxidative stress parameters: In order to detect lipid perioxidation malondialdehyde (MDA), parts of kidney tissues were homogenized in a saline solution (0.9%), centrifuged for 15 minutes at 3000 rpm, and the supernatant was stored at -20 °C [12], superoxide dismutase (SOD) as designated by Nishikimi' technique [13] and antioxidants enzyme as reduced glutathione (GSH) [14]. All the above kits provided by Bio diagnostic, Cairo, Egypt (Catalog Number: MD 25 29, Catalog Number: GR 25 11, Catalog Number: SD 25 21, correspondingly).

Histological and immunohistochemical examinations: Experimental and control animals' kidneys were carefully removed, preserved in 10% neutral formalin, dried, cleaned in xylene, then inserted in melted paraffin wax. At 5μm, paraffin block sections were created, enabling Hematoxylin and Eosin (H&E) staining to detect the general histological structure. Masson's trichrome-stained sections in order to detect the collagen fibers in tissues [15].

Immunohistochemistry analysis of Bax and PCNA: Kidneys were sliced into paraffin sections each is 5 μm thick, then placed into positively charged slides, deparaffinized, and rehydrated in a decreasing series of alcohols. Then, using 1% diluted H_2O_2 in PBS, for a period of 10 minutes the activity of endogenous peroxidase was impassable. Following slide cleaning with PBS with 1% bovine serum albumin (BSA), 3% powdered skimmed milk in PBS was used to suppress background stains.

For labeling of BAX the kidney slices were incubated for an entire night at 4 °C with Bax monoclonal antibody. For PCNA labeling, the sections were incubated in anti-PCNA (monoclonal antibody against PCNA, diluted 1:50 in PBS; Dako, Denmark) for 10–12 h. The sections were treated with biotinylated antibody for 45 minutes at room temperature after being rinsed three times for five minutes each in PBS plus 1% BSA [16]. (Positive reaction: BAX: brown cytoplasmic reaction, PCNA: brown nuclear reaction).

Morphometrical study: Morphometric analysis was performed by capturing images using a Leica light microscope (DM500, Switzerland) and subsequently analyzing them with "ImageJ" software (version 1.48v, National Institutes of Health, Bethesda, Maryland, USA). For each slide, 10 picked up at random, non-overlapping fields were studied at a 400x magnification power to estimate the average area % of collagen fibers, average area percentage of positive immunohistochemical staining for BAX and mean number of PCNA-immunopositive cells.

Ethical consideration: Every experimental procedure followed Official Animal Care and Practice Committee's recommendations and received approval from Benha Faculty of Medicine, Benha University, Egypt, number RC 3- 8 -2024. The study adhered to the Helsinki Declaration throughout its execution.

Statistical analysis

Version 20 of the Statistical Package for the Social Sciences (SPSS) software (SPSS Inc., Chicago, Illinois, USA) was used to analyze the data that had been gathered. If the P value was < 0.05, it was deemed significant and if it was < 0.001 it was considered extremely significant. The mean ± SD was used to express all data.

RESULTS

Biochemical results: The results in table (1) indicated that serum levels of urea and creatinine in group II were considerably higher than those in group I. Dissimilar to group II, each of group III as well as group IV presented considerable decrease in their levels. Interestingly, group V noticeably returned all the altered parameters to levels near to that of the control rats.

Table (1): Comparisons of the serum levels of urea and serum levels of creatinine in the several groups under investigation using ANOVA (analysis of variance) test (Mean ±SD)

Variable	Group I Control **(n=10)**	Group II MSG **(n=10)**	Group III MSG+ CUR **(n=10)**	Group IV MSG + HESP **(n=10)**	Group V MSG +CUR+HESP **(n=10)**
serum Urea (mg/dl)	38.3±2.9	98.6±8.9 a, c, d, e**	57.5±5.4 b*	54.4±4.6 b*	46.7±3.8 b*
Serum Creatinine (mg/dl)	0.41±0.02	1.37±0.09 a, c, d, e**	0.60±0.06 b*	0.66±0.04 b*	0.51±0.03 b*

P:p-value **. *** significant **:**(p < 0.05).****:** highly significant (p< 0.001). Values are presented as mean ± SD, a: significantly highly different with the control group (p<0.001). b: significantly altered with the MSG group (p < 0.05). c: significantly altered with the MSG +CUR group (p < 0.05). d: significantly altered with MSG+HESP group. (p < 0.05). e: significantly altered with MSG+ CUR+ HESP group (p < 0.05).

Oxidative stress indicators: According to the indicated data in table (2), group II exhibited substantial surge in tissue MDA levels and a concurrent decline in tissue GSH and SOD in comparison with group I. Dissimilar to group II, groups III and IV presented considerable reduction in the MDA level and momentous increase of GSH level and SOD level. Group V's combination significantly returned all the altered parameters to levels near to that of control animals.

Table (2): Comparisons of the levels of oxidative markers in the several groups under investigation using ANOVA (analysis of variance) test (Mean ±SD)

Variable	Group I Control (n=10)	Group II MSG (n=10)	Group III MSG +CUR (n=10)	Group IV MSG+HESP (n=10)	Group V MSG+CUR+ HESP (n=10)
MDA (nmol/g)	0.74±0.06	3.85 ± 0.22 a, c, d, e**	1.19 ± 0.09 b*	1.15 ± 0.09 b*	0.8 ± 0.09 b*
SOD (units/mg protein)	27.8 ±0.23	18.9 ± 0.49 a, c, d, e**	25.3 ± 0.16 b*	24.9 ± 0.21 b*	27.4 ± 0.15 b*
GSH (nmol/g)	15.4 ± 1.5	5.2 ±0.42 a, c, d, e**	10.7 ± 0.78 b*	13.2 ± 1.12 b*	14.2 ± 1.11 b*

MDA: Malondialdehyde, SOD: Superoxide dismutase, GSH: Glutathione, n: number, SD: standard deviation, nmol: number of moles, mmol: mili mole, U/g: microgram, **SD**: Standard deviation. **P**:p-value **. *** significant **:**($p < 0.05$). ****:** highly significant ($p<0.001$). Values are offered as mean ± SD, a: Significantly highly altered with the control group at ($p<0.001$). b: Significantly altered from the MSG group at ($p < 0.05$). c: Significantly altered with the MSG +CUR group ($p < 0.05$). d.: Significantly altered with MSG+HESP group. ($p < 0.05$). e: Significantly altered with MSG+ CUR+ HESP group ($p < 0.05$).

Histological Examination

Hematoxylin and eosin staining results:

A characteristic histological architecture of glomeruli with a limited renal glomerular capsular space was seen in the control group's rat renal cortex.

The cells lining the distal tubules showed less acidophilic cytoplasm, while the cells lining the proximal convoluted tubules had vesicular rounded basally located nuclei (Figure 2A). The renal cortex of rats in the MSG-treated group showed evident pathological alterations including atrophy of some glomeruli that was segmented, others appeared markedly hypertrophied with dilated congested capillaries. A wide capsular space around the glomeruli and tubular cells exhibited vacuolated cytoplasm with detachment from the basement membrane were also noted. In addition, there was interstitial inflammatory cellular infiltration and the presence of pyknotic nuclei in some tubules. Moreover, large blood vessel with thickened wall with the lining endothelium was irregular (Figure 2B & 2C). The renal cortex of rats treated with curcumin alongside MSG showed a partial restoration of normal renal architecture. However, some glomeruli still exhibited widened capsular spaces. The proximal and distal convoluted tubules largely retained their normal histological features, though vacuolations were observed within the epithelial lining of certain tubules (Figure 2D).

In the group treated with hesperidin alongside MSG, the kidney exhibited a nearly normal architecture, with the glomerulus showing typical histological features and a narrow capsular space around it, some tubules contain hyaline cast (Figure 2E). In group V, the renal cortex of rats appeared similar to the control group, displayed a typical histological structure of the glomeruli with a constricted capsular space and normal tubules (Fig 2F).

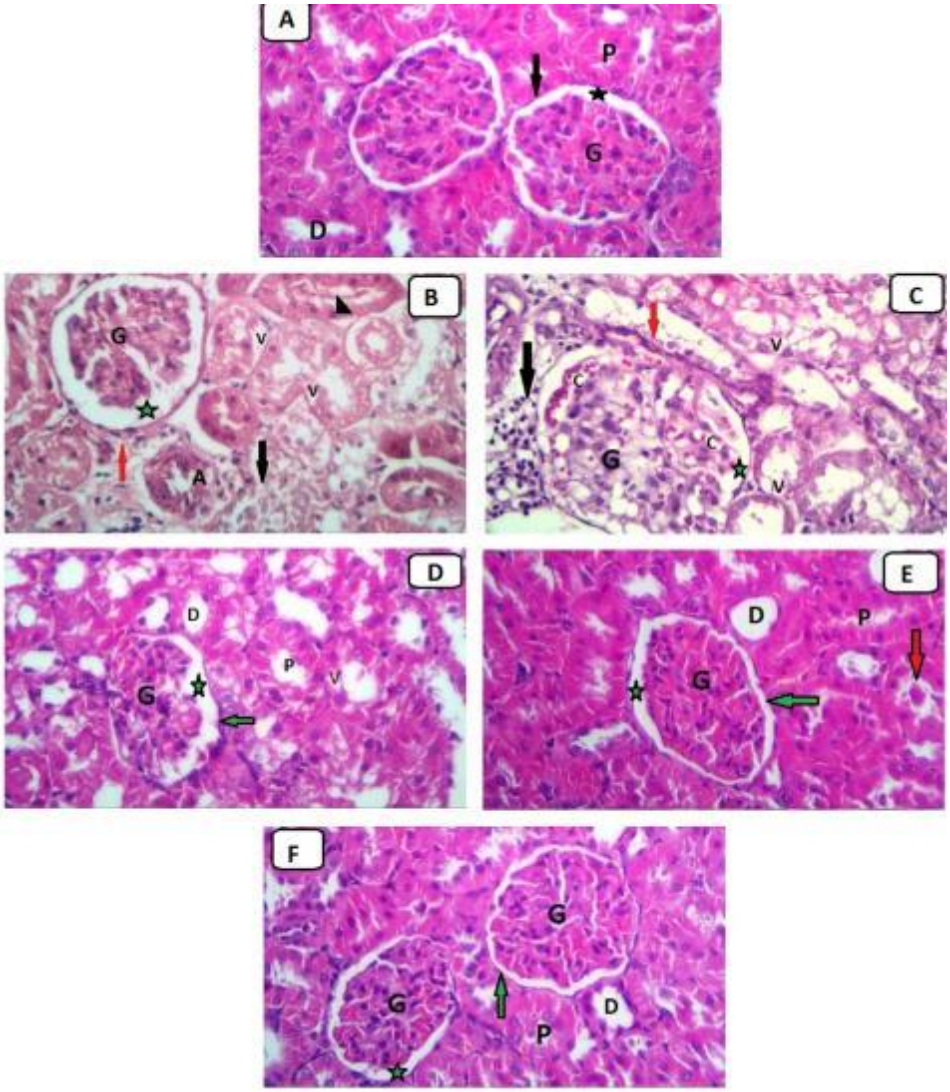

Figure (2): Photomicrograph of a transverse section of renal cortex of adult male albino rat: **[A]**: The control group displays: The renal corpuscle with the glomerulus (G), Bowman's space (star), and Bowman's membrane in a normal look **(black arrow)**, proximal tubules (P) and distal tubules (D). **[B]:** Group II displaying: Tubular degeneration **(black arrow)** and enlarged capsular space (star) with shrunken lobulated glomeruli **(G)**, pyknotic nuclei **(arrow head)**, tubular cells exhibited vacuolated cytoplasm with detachment from the basement membrane (V). The artery (A) showed a thickened wall and is encircled by inflammatory cell infiltration (red arrow) **[C]:** Group II demonstrated a hypertrophied glomerulus (G) with markedly dilated congested capillaries (C) and a reduced Bowman's space (star). Infiltration of inflammatory cells (black arrow) was evident, along with tubular cells showing vacuolated cytoplasm (V) and degenerated epithelial lining accompanied by tubular dilatation (red arrow**) [D]**: Group III displays: The glomerulus (G), Bowman's space (star), proximal convoluted tubules (P), and distal convoluted tubules (D), with some tubular cells exhibiting vacuolated cytoplasm. **[E]**: Group IV displaying: Normal appearance of the renal corpuscle comprising the glomerulus (G), Bowman's space (star), proximal tubules (P) and distal tubules (D). Bowman's capsule (green arrow), hyaline cast (red arrow). **[F]**: Group V showing: Normal glomerulus (G), Bowman's space (star), Bowman's capsule (green arrow), proximal tubules (P) and distal tubules (D). (H&E x400).

Masson's trichrome staining results: The control group (group I) exhibited very fine collagen fibers adjacent to the glomerulus and around renal tubules **(Figure 3A).** In contrast, the MSG treated group (group II) demonstrated copious collagen fibers adjoining the renal glomerulus and nearby renal tubules **(Figure 3B).** Group III presented moderate quantity of collagen fibres **(Figure 3C).** However, the concomitant administration of hesperidin with MSG (group IV) displayed little collagen fibers nearby the glomeruli and renal tubules **(Figure 3D).** Finally, Collagen fibers were found in very little levels between the renal tubules and around glomerulus in group V **(Figure 3E).** The statistical analysis of the area percentage of collagen fibers in each experiment group supported these findings.

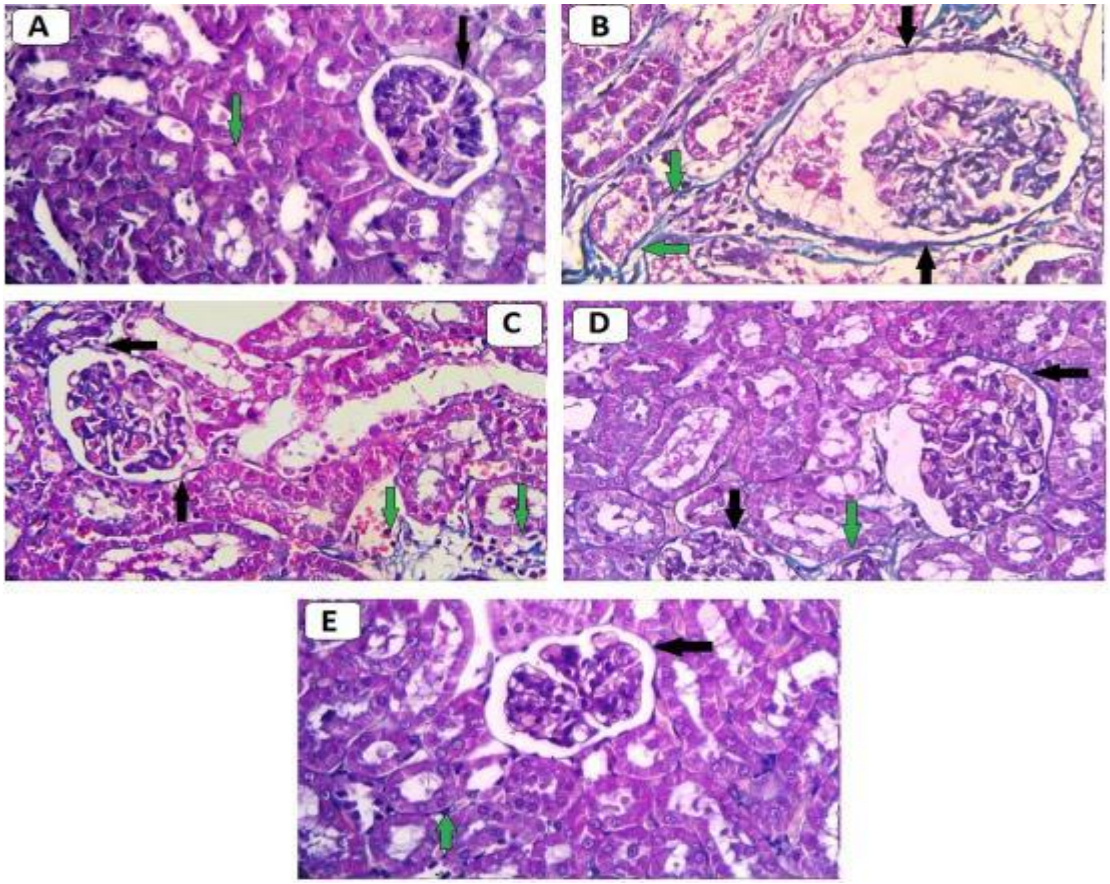

Figure (3): A Photomicrograph of a transverse section in renal cortex of adult male albino rat displays **[A]**: Control group exhibited: Very fine collagen fibers nearby the glomerulus (black arrow) and among the tubules (green arrow) **[B]** Group II demonstrating: Significant collagen fiber invasion around glomerulus(black arrow) and in between renal tubules(green arrow)**.[C]** Group III: Demonstrating moderate collagen fibers deposition nearby glomerulus (black arrow) and in between renal tubules(green arrow). **[D]** Group IV showing: Minimal collagen fibers deposition around the glomerulus (black arrow) and in between renal tubules (green arrow)**. [E]** Group V demonstrating: very minimal collagen fibers nearby glomerulus (black arrow) and in between renal tubules (green arrow). (Masson trichrom stain X400).

Immunohistochemical results: BAX: Group I exhibited negative BAX immuno-expression in the cytoplasm of glomerulus and renal tubular epithelium (Figure 4A). Monosodium glutamate group presented a strong positive BAX immunoreaction in the cytoplasm of the renal tubular epithelium and in the glomerulus (Figure 4B). Group III showed weak immunoreaction for BAX (Figure 4C). Group IV showed weak immunoreaction for BAX (Figure 4D). Group V showed negative immunoreaction for BAX (Figure 4E).

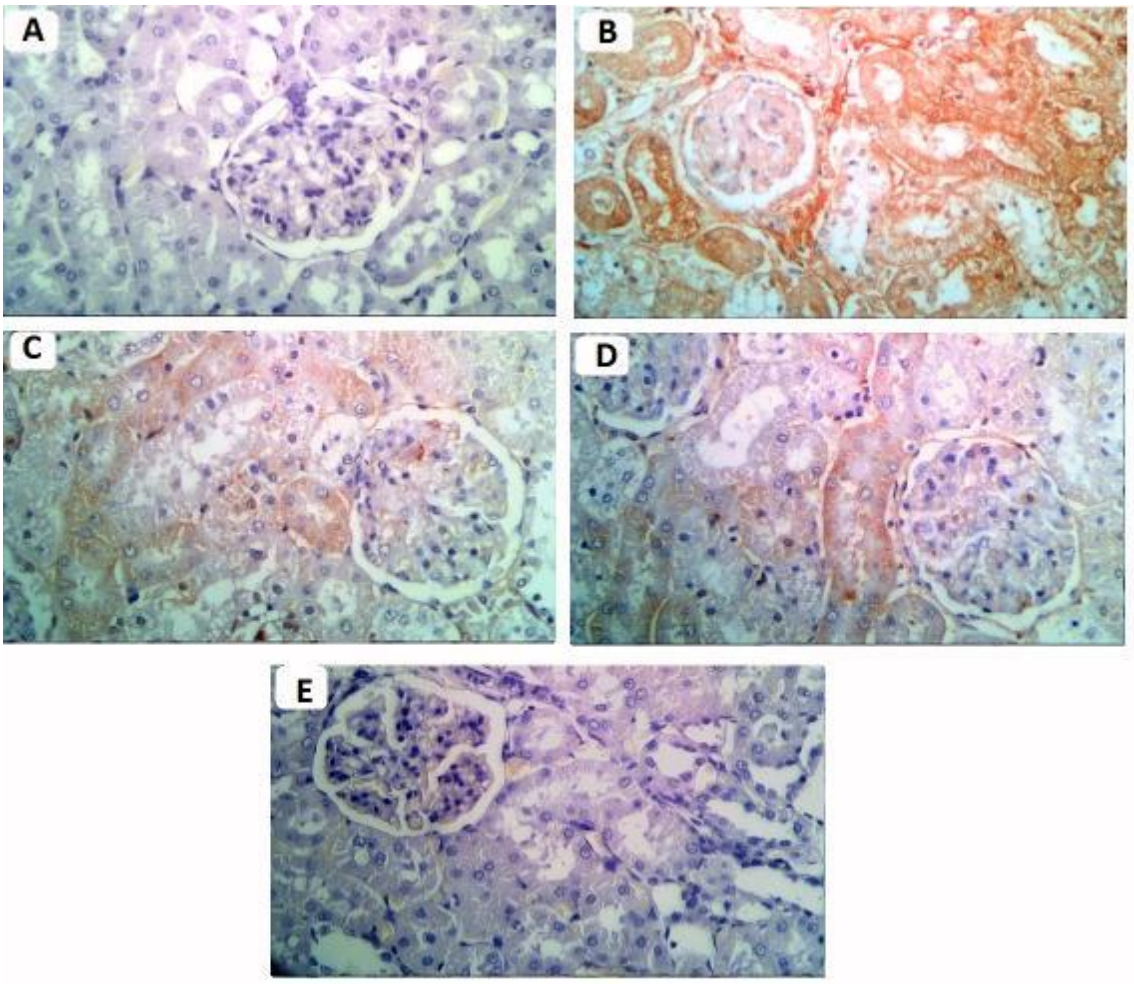

Figure (4): A Photomicrograph of a transverse section in renal cortex of adult male albino rat displays **(A):** The control group **(**Group I): Showed negative immuno-expression of BAX in the glomerulus and renal tubular cytoplasm. **(B):** Group II displayed: A strong positive immunoreaction for BAX in the glomerulus and renal tubular cytoplasm. **(C)**: Group III revealed: Moderate immunoreaction for BAX in the glomerulus and renal tubular cytoplasm. **(D)**: Group IV showed: Mild immunoreaction for BAX. **(E)**: Group V demonstrated: Negative immunoreaction in the cytoplasm of glomerulus and renal tubular epithelium. **(BAX immunostaining with counter stain hematoxylin ×400)**

PCNA: Group I, the control group stained with PCNA immuonostain displayed negative immunoreaction in the nuclei of cells lining the glomerulus and renal tubules (Figure 5A). MSG group showed a strong positive immunoreaction for PCNA in glomerulus, cells lining to renal tubules and in nuclei of inflammatory cells (Figure 5B). MSG + curcumin-treated group revealed moderate immunoreaction for PCNA. MSG + hesperidin-treated group showed mild immunoreaction for PCNA (Figure 5D). MSG+ curcumin + hesperidin-treated group showed very weak immunoreaction for PCNA (Figure 5E).

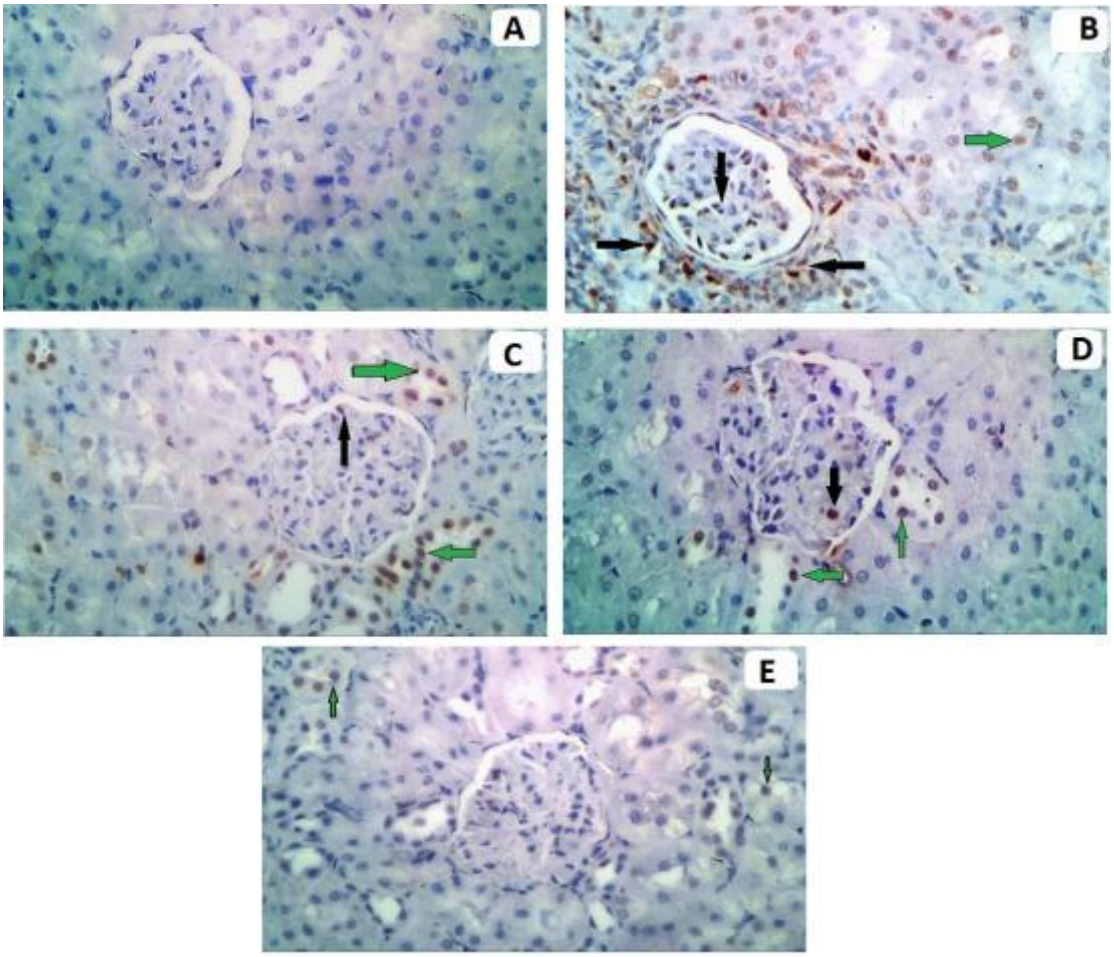

Figure (5): Photomicrograph of a transverse section of renal cortex of adult male albino rats: **[A]**: Group I, the control group, showed a negative PCNA immunoreaction. **[B]:** Group II presented strong PCNA immunoreaction in glomerulus and renal tubules. **[C]**: Group III displayed moderate PCNA immunoreaction in glomerulus and renal tubules. **[D]:** Group IV presented mild PCNA immunoreaction**. [E]:** Group V demonstrated: very mild PCNA immunoreaction in renal tubules (PCNA X400).

Morphometric results: The typical area percent of collagen fiber deposition in group II was substantially higher than in group I. Collagen fiber deposition was significantly lower in groups III and IV matched to group II. Group V had substantially less collagen fiber deposition than groups II, III, and IV. Group II had a significantly greater average area percent of BAX immune-expression than group I. On the other hand, compared to group II, the average area % significantly decreased in groups III and IV. Group V had a substantially lower value than groups II, III, and IV. The mean area percent of PCNA immunoreaction was significantly higher in group II than in group I. However, group III and group IV displayed significantly lower statistics than group II. It was much lower in group V than in groups II, III, and IV (Table 3).

Table (3): Displaying the average area percentage and standard deviation of the distribution of collagen fiber deposits, BAX, and PCNA across all groups under study

mean area % and SD of	**Group I Control**	**Group II MSG**	**Group III MSG +CUR**	**Group IV MSG+HESP**	**Group V MSG+CUR+ HESP**
collagen fibers	2.3 ± 1.1	41.3 ± 3.6 a,c,d & e**	12.4 ± 0.8 b*	14.3 ± 1.4 b*	2.8 ± 2.1 b,c & d*
BAX immunoreaction	4.3±1.3	46.2 ± 4.6 a,c,d & e**	16.4 ± 2 b*	17.4 ± 1.7 b*	6.3 ± 2.6 b,c & d*
PCNA	1.6±0.5	38.2± 8.6 a,c,d & e**	18.6 ± 0.7 b*	13.5 ± 0.9 b*	3.6 ± 0.6 b,c & d*

SD: standard deviation. **P**: p-value *: Significant (P<0.05). **: Highly significant (p<0.001). a: significantly highly different with the control group (p<0.001). b: significantly altered with the MSG group (p < 0.05). c: significantly altered with the MSG +CUR group (p < 0.05). d: significantly altered with MSG+HESP group. (p < 0.05). e: significantly altered with MSG+ CUR+ HESP group (p < 0.05).

DISCUSSION

One of the furthermost widely held food flavors in the world is MSG. It is employed as a taste enhancer in contemporary nutrition all over the world [17]. Curcumin is a herbal remedy with several positive therapeutic benefits that is utilized in medicine [18]. The phytoflavanone glycoside hesperidin (HSP) is present in citrus fruitlets like lemons and oranges. Its pharmacological properties are numerous [19].

The MSG-treated group (group II) in our investigation showed elevated serum levels of urea and creatinine. This is in line with research by **Abdelhamid *et al.*** [20], which showed that in comparison with control groups, MSG significantly raised serum level of urea, creatinine, and uric acid concentrations**.** In contrast to group II, serum level of urea and serum level of creatinine were minor in groups III and IV. While in group V serum level of urea and serum level of creatinine were considerably lower and were comparable to those in group I. According to **Ahmed *et al.*** [21] curcumin's capacity to lower plasma urea levels results from an increase in renal urea clearance. **Abd-Eltawab *et al.*** [9] discovered that HSP shielded the kidneys by depressing serum levels of urea and creatinine because it is a potent antioxidant [9].

In our study, the MSG-treated group (group II) exhibited a decrease in SOD and GSH and an increase in levels of MDA compared to the control group (group I). This is matched with the research of **Paul *et al.*** [22] who observed decreased kidney activity of glutathione-S-transferase (GSTs), glutathione (GSH), superoxide dismutase (SOD), catalase and increased MDA level following MSG administration. Also **Sharma *et al.*** [23] showed that renal tissue treated with MSG had higher levels of lipid peroxidation indicators such conjugated dienes and malondialdehyde (MDA) [23]. However, in this investigation, groups III and IV showed a large rise in GSH and SOD levels and a considerable drop in MDA levels. Interestingly, the addition of curcumin and hesperidin to MSG-treated rats in group V significantly returned all of the changed parameters to values identical to those of group I. Curcumin dramatically improved the SOD and CAT activities while lowering the high MDA levels, demonstrating excellent antioxidant and free radical scavenging characteristics. Since free radicals are more likely to develop than be detoxified by antioxidants, curcumin protected against oxidative stress damage [24]**. Abd-Eltawab *et al.*** [9] claimed that the restoration of nearly normal levels of GSH and MDA along with CAT activity in the tissues of kidney and liver proved HSP's antioxidant capacity.

In the current experiment, group II H & E-stained sectors exhibited atrophy of some glomeruli, which was segmented and others appeared markedly hypertrophied with dilated congested capillaries. A wide capsular space around the glomeruli and tubular cells exhibited vacuolated cytoplasm with detachment from the basement membrane and the presence of pyknotic nuclei in some tubules were also noted. In addition, there was interstitial cellular infiltration. This consistent with **Adam *et al.*** [17] who demonstrated that MSG caused numerous histological changes in the participants' kidneys, such as renal tubule dilatation and degeneration or necrosis of epithelial cells lining to the renal convoluted tubules and the glomeruli**.** Also **Mohammed *et al.*** [25] found that adult rats treated with MSG had vascular congestion, hyaline and tubular cellular casts, and patchy interstitial inflammatory infiltration in their kidney tissue**. Sharma *et al.*** [23] clarified the nephrotoxic properties of MSG by a number of processes, including the generation of ROS in the kidney following exposure to MSG, which was considered to be a significant sponsor in the nephrotoxic properties that resulted in cellular and functional damage**.**

Group III in the current investigation showed a partial return to normal renal architecture. Nonetheless, enlarged capsular gaps were still seen in

certain glomeruli. Vacuolations and degenerations were observed in several renal tubules. Group IV showed a constricted Bowman's space, cortical tubule normal epithelial cells, and a nearly normal glomerulus with well-defined borders. It is interesting to see that group V rats showed normal renal tubules and glomeruli, just like the control group. According to **Abdelhamid *et al*.** [20] curcumin inhibits inflammatory cytokines, avoids lipid peroxidation, increases the manufacture of several cytoprotective and antioxidant proteins, and lessens tissue damage brought on by free radicals. **Küçükler *et al.*** [26] found that hesperidin administration decreased the effects of the pesticide chlorpyrifos on rats, including renal congestion, intertubular bleeding, degeneration, and necrosis alterations. According to the authors, hesperidin's antioxidant qualities account for its nephron-protective effects.

The MSG-treated group in this study displayed a notable infiltration of collagen fibers between the renal tubules and around the glomerulus in contrast to the control group. This is covenant with **Sampson *et al.*** [27] that oxidative stress brought on by consuming too much MSG causes kidney fibrosis because reactive oxidants cause fibroblasts to differentiate into myofibroblasts.

According to **Sarhan** [28], the underlying causes of this fibrosis include oxidative stress and the creation of ROS. These chemicals have the ability to induce fibroblasts to develop into myofibroblasts, which upsurges the quantity of collagen fibers deposited in the tissues of the kidney, liver, and testicles**.** Additionally, **Sharma *et al.*** [23] found a connection between renal fibrosis and prolonged MSG consumption**.** In this investigation there were moderate to mild quantities of collagen fibers between the renal tubules and glomeruli in groups III and IV, whereas group V showed very little. **Abdelhamid *et al.*** [20] found that the group treated with MSG + curcumin had a considerably lower mean area percentage of collagen fibers.

The renoprotective effect of curcumin is mediated by many mechanisms. Lowering oxidative stress by inhibiting the creation of ROS and encouraging the transcription of genes for antioxidant enzymes. By lowering inflammatory mediators, curcumin can help lessen the inflammatory process. It also lowers the cytokines that cause kidney fibrosis [29]**.** Supplementing with hesperidin inhibits renal immune stimulation and interstitial fibrosis between the tubules. Its defending effect on the kidney may be attributed to expansion of the mesangial matrix, extreme stimulation of the intrinsic immune system, comprising the system of complement, and amelioration of renal tubule damage [30].

In association to the control group, the MSG-treated group in this study displayed much stronger positive Bax immunoreactions in the glomeruli and renal tubules. These findings supported the findings of **Abass and Abd El-Haleem** [31] who found that MSG can alter the pattern of Bax protein expression in some tubular epithelial cells as well as glomerular endothelial cells**.** According to **Sarhan** [28], MSG can cause oxidative stress by inducing both internal and extrinsic apoptotic pathways, which can result in cell death [28]**.**

In this study, group V displayed negative Bax immunoreaction in renal tubules and glomeruli that was almost identical to control, but groups III and IV displayed moderate to mild Bax positive immunoreactions in these areas respectively. Curcumin dramatically decreased the quantity of TUNEL-positive cells by triggering the PI3K/Akt pathway. This entailed blocking the tumor necrosis factor-gamma signaling pathway, decreasing the release of pro-apoptotic caspases, and lowering the Bax/Bcl-2 ratio [32]**.** Co administration of hesperidin with Malathion that prompted renal damage, reduced apoptotic markers (caspase-3, Bax), and improved the antiapoptotic marker (Bcl-2) in comparison with the Malathion-treated group [33]**.**

In this investigation, the MSG-treated group had noticeably more positive PCNA immunoreactions in the glomeruli and renal tubules than the control group. While, the renal tubules of group V showed a very mild PCNA immunoreaction and the glomeruli and renal tubules of groups III and IV showed moderate to mild PCNA positive immunoreactions respectively.

This is consistent with **Youreva *et al.*** [34] findings that following the toxic insult linked to MSG, there were more PCNA immune-reactive cells as a result of increased mitotic action in the glomerulus and in cells lined renal tubules. Curcumin treatment progressively reduced the expression of immune-reactivity of PCNA. Curcumin's anti-proliferative action resulted from its suppression of the activity of protein kinases and the inhibition of growth factor signals' mitogenic impact on hypertrophic cells. Furthermore, by causing DNA damage and halting the cells at different stages of the cell cycle, which results in apoptosis, curcumin can prevent the development of malignant and aberrant cells.

HSP may prevent hepatic and renal toxicities through inhibition of cellular proliferation, suppression of various inflammatory and apoptotic biomarkers, modulation of cellular antioxidants which may be enzymatic or non-enzymatic, and reduction of proliferating cell nuclear antigen (PCNA) [9]. In accordance with prior research by **Gelen *et al.*** [35 combined curcumin and hesperidin have a synergistic impact on biochemical parameters and the histological damaging effects of 5-FU prompted renal injuriousness in mice. It is thought that these effects result from their anti-inflammatory and antioxidant possessions. By increasing the anti-oxidant influence and lowering ROS-intervened 8-OHdG levels, combined treatment helps to avoid oxidative DNA damage. Thus, according to our research, when curcumin and hesperidin are

combined, the results are better than when either substance is used alone, and, hence, it is suggested for protection from the risks of MSG on the kidney.

CONCLUSION

Adult male albino rats' kidneys had various structural and metabolic alterations as a result of monosodium glutamate intake. These changes were reversed when hesperidin and curcumin were given separately but when taken combined, curcumin and hesperidin shield kidney tissue against excess monosodium glutamate.

RECOMMENDATION

Further researches on the consequence of monosodium glutamate on other human organs are recommended.

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