Original Article

Ameliorative Effects of *Punica Granatum* Juice and Bee Pollen Against Hepatotoxicity and Renal Toxicity Induced by Monosodium Glutamate in Adult Male Albino Rats

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ABSTRACT

Introduction: Monosodium glutamate (MSG) is a worldwide consuming food additive that has been shown to be health hazardous, especially, on the Liver and kidneys that among the most vital body organs.

Aim of the Study: Evaluation the possible ameliorative effects of *Punica granatum* juice (PJ) and Bee pollen (BP) against MSG hepatic and renal biochemical and histological disorders.

Materials and Methods: 30 adult male albino rats were randomly divided into 5 groups (n= 6 each). In the 1st (normal) group, rats were orally received distilled water for 10 weeks. All the other groups were orally received MSG (2.4g/kg b.w.) daily for 4 weeks. After that the 3rd group was orally received PJ (4ml/kg b.w.), the 4th group was orally received BP (200mg/kg b.w.) and the 5th group was orally received PJ (4ml/kg b.w.) + BP (200mg/kg b.w.) daily for 6 weeks. Blood and tissue samples were collected for biochemical assays and histopathological studies.

Results: Biochemically, MSG caused significant increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels, significant decrease in serum albumin and total protein, and significant increase in serum total Cholesterol (TC), triglycerides (TGs), low density lipoprotein (LDL) and very low-density lipoprotein (VLDL). However, high density lipoprotein (HDL) was significantly decreased. Also, serum creatinine, urea and uric acid were significantly increased. Besides, oxidative damage evidenced by significant reductions in the hepatic and renal total antioxidant capacity (TAC) and significant increase in their malondialdehyde (MDA) levels was reported. Histopathologically, MSG caused severe hepatic and renal alterations. Contrarily, all the mentioned disorders were alleviated after PJ and BP administration.

Conclusion: MSG caused hazardous effects on the liver and kidneys. However, the use of PJ and BP ameliorated these toxic effects in the mentioned parameters.

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Key Words: Bee pollen, hepatotoxicity, monosodium glutamate, *punica granatum* juice, renal toxicity.

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INTRODUCTION

Food additives (organic chemicals) are commonly added to almost all processed food for improving its taste quality. MSG, commonly known as fifth taste, is one of the openly used food additives as a flavor enhancer that may present without appearing on the synthetic food labels[1]. It is mostly found in many types of manufactured food such as marinated meats, prepared flavored chips, sausages and luncheon chicken, snacks, seasoned chicken and vegetarian burgers. However it is considered toxic to experimental animals and humans, especially if it is consumed with over amounts or for a long time. The body organs have many receptors of glutamate, thus high amounts daily consumption of MSG impairs over stimulation of these receptors resulting in many hazardous alterations in these organs especially, liver and kidneys considering that they are the main organs responsible for xenobiotic degradation, detoxification and excretion, respectively. Moreover, glutamate in high doses produce oxidative damage that leads to biochemical, physiological and histological disturbances in experimental animals[2].

On the other hand, it is well known that antioxidants from natural sources have few side effects relative to the synthetic antioxidants. Here in our study, we used two of the most important and valuable natural products, pomegranate juice (PJ) and bee pollen (BP), against the toxicity of MSG. Pomegranate, *Punica granatum*, is a critical fruit which is commonly grown in subtropical and tropical countries. It belongs to the family Punicaceae[3]. PJ possesses many biological roles among which, its antioxidant activities that relates to its high contents of anthocynins, tannins, as well as flavonoids[4]. Moreover, it was documented that 250 ml glass of PJ provides approximately 50% of daily recommended vitamins E, A and C[5].

BP is a product of honey bees that contains various and essentially nutrients for human body organs. BP can

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be defined as pollen grains, collected by the honeybee workers from various plant sources that mixed with nectar, enzymes, honey, beeswax and honeybee salivary secretions[6]. It possesses not only antibacterial and antifungal biological activities, but also strong antioxidant activities[7,8]. It also plays a vital role in inducing damaged tissues regeneration[9].

MATERIALS AND METHODS

Drugs and chemicals

MSG, its purity (99.7%), was purchased from AVI-CHEM LABORATORIES Pvt. Ltd. (A-221,Amargain Industrial Complex, Opp. S.T. stand, LBS marg, Khopat Thane (w) Mumbai, Maharashtra, India). MSG was orally administered to the rats as (2.4 gm/kg b.w.) (15% of LD50 of MSG)[10]. Pomegranate (*Punica granatum*) was subjected to peel off, then squeezed for collecting its fresh juice. PJ doses were prepared freshly daily in labeled clean containers and were administered as (4 ml/kg b.w.), which is an optimal concentration according to[11]. Bee pollen (BP), supplied by the Faculty of Agriculture, South Valley University, Qena, Egypt. BP was orally administered as 200 mg/kg b.w. (in distilled water) which is considered an optimal concentration according to[12].

Animals

Thirty adult male albino Wister rats aged 13–14 weeks were housed in the Animal House, Faculty of Science, South Valley University, Qena, Egypt. Their body weights were ranged 190–210 gm. They were housed during all the experimental period under a controlled environment (12-h light/dark cycle, 21–25 ^{o}C and 55% relative humidity) in polypropylene cages. Water was provided ad libitum and standard commercial pellets were used as food. During the entire course of the experiment, all other conditions relating to the rats health were maintained. The local institutional guidelines were followed in our experimental protocol that approved by the Animal Ethical Committee (published by the Faculty of Science, South Valley University under code No. 006/01/24), Qena, Egypt.

Experimental design

Before conducting the experiments, rats were housed and observed for 14 days for exclusion out of any inter current infections and for acclimatization to the new surrounding conditions. After that, rats were divided randomly into 5 groups, (n=6 each). The normal group orally received distilled water (0.5 ml/kg b.w.) daily for 10 weeks. MSG group orally received MSG (2.4g/kg b.w. in 0.5 ml distilled water) daily for 4 weeks. MSG+PJ group orally received MSG (2.4g/kg b.w.) daily for 4 weeks and then orally received PJ (4 ml/kg b.w.) daily for 6 weeks. MSG+BP group orally received MSG (2.4g/kg b.w.) daily for 4 weeks and then orally received BP (200 mg/kg b.w. in 0.5 ml distilled water) daily for 6 weeks. MSG+PJ+BP group orally received MSG (2.4g/kg b.w.) daily for 4 weeks and then orally received (4 ml/kg b.w. of PJ and 200 mg/kg b.w. of BP) for 6 weeks.

Sample collection

24 hours after the last treatment, using micro capillary glass tubes, blood samples were collected in clean plain tubes from the retro-orbital sinus of rats. Blood samples were allowed to clot at room temperature. After an hour they were centrifuged for half an hour at 3000 rpm to separate the clear sera. The sera were collected in clean labeled Eppendorf tubes which after that stored at -20 °C for subsequent hepatic and renal biochemical assessments. Then, the rats were euthanized, and their livers and kidneys were carefully dissected. Subsequently, the organs were thoroughly washed with 0.9% sodium chloride solution. Samples were quickly divided into two portions; one portion (from each organ) was frozen at -80 ^{o}C for TAC and MDA assays, and the later portion (from each organ) was fixed in 10% neutral buffered formalin for histopathological examinations.

Biochemical analysis

Serum biochemical analysis

Liver functions including serum AST, ALT, albumin and total protein levels, as well as serum lipid profile (TC, TGs, LDL, VLDL and HDL) were measured. Also, kidney functions including creatinine, urea and uric acid were assayed by means of T60 UV-visible spectrophotometer. Kits were purchased from (Bio-Diagnostic, Egypt).

Total antioxidant capacity (TAC) and malondialdehyde (MDA) assays of liver and kidney tissue homogenates.

For TAC and MDA estimations, frozen liver and kidney samples were homogenized using chilled Tris-HCl buffer (pH 7.4), and then were centrifuged for half an hour at 4 oC at 4000 r/min. Supernatant from tissue homogenates were collected and used for TAC and MDA estimations by means of T60 UV-Visible spectrophotometer. Kits were purchased from Bio-Diagnostic, Egypt.

Histopathological studies

Liver and kidney were fixed in neutral buffered formalin, and were then washed in 70 % ethyl alcohol for removing the fixative. Samples were then dehydrated in ascending series of ethyl alcohol (70 %, 80 %, 90 %, 100 % 1st, 100 % 2nd). Subsequently, samples were cleared in methyl benzoate, followed by embedding in paraffin wax[13]. 5µm thickness paraffin sections were cut and stained in hematoxylin and eosin stain for general histopathological studies.

Statistical analysis

All data were analyzed by means of prism computer software program. One-way ANOVA analysis of variance was used to determine the statistical differences for each parameter among the different groups. Least significant difference (LSD) was used to test the difference between more than two groups. Means ± standard deviation of means (Mean±S.D) express the degree of results variability. If *P* value > 0.05, then results were considered statistically non-significant. If *P value* < 0.05, then results were considered statistically significant.

RESULTS

Biochemical results

Liver functions indexes in the serum of the experimental groups

The levels of serum AST and ALT were significantly increased in the MSG group compared to the normal group. However, in the MSG+PJ, MSG+BP, and MSG+PJ+BP groups, there was a significant decrease in AST and ALT levels compared to the MSG group. On the other hand, our results showed a significant decrease in serum albumin and total protein levels in the MSG-treated group, while serum albumin and total protein were significantly increased in the MSG+PJ, MSG+BP, and MSG+PJ+BP groups relative to the MSG group. However, when compared with the normal group, all the results in the MSG+PJ, MSG+BP, and MSG+PJ+BP groups recorded remarkable improvements with non-significant differences (Table 1).

Lipid profile indexes in the serum of the experimental groups

The results showed significantly higher mean level of TC, TGs, LDL and VLDL levels in MSG compared to the normal group. Also, their means in the MSG+PJ, MSG+BP and MSG+PJ+BP groups were significantly lower than those in MSG group. Meanwhile, there was a significant lower mean level of HDL level in MSG group compared to the normal group. However, HDL mean levels in the MSG+PJ, MSG+BP and MSG+PJ+BP groups were significantly higher than those in MSG group. However, when compared with normal, all the result in MSG+PJ, MSG+BP and MSG+PJ+BP groups recorded a remarkable improvement with non-significant differences (Table 2).

Kidney functions indexes in the serum of the experimental groups

The results showed significantly higher means of creatinine, urea and uric acid levels in MSG group than in the normal group. Also, their means in the MSG+PJ, MSG+BP and MSG+PJ+BP groups were significantly lower than those in MSG group. At the same time, their levels in MSG+PJ, MSG+BP and MSG+PJ+BP groups recorded a remarkable improvement with non-significant differences (Table 3).

Hepatic and renal TAC and MDA levels among the experimental groups

The liver and kidney tissue homogenates of the MSG group showed significantly higher means of MDA and significantly lower means of TAC levels compared to the normal group. However, MSG+PJ, MSG+BP and MSG+PJ+BP groups showed significantly lower means of MDA levels and significantly higher mean of TAC than the MSG group. At the same time, the means of MDA values in MSG+PJ, MSG+BP and MSG+PJ+BP groups were non-significantly increased and the means of TAC levels were non-significantly decreased compared to the normal group (Table 4).

Histopathological results

In the normal group, the liver exhibited normal structure of hepatic lobules with normal structure of hepatic cells arranged in linear cords between a blood sinusoids, and a central vein (Figure 1). Likewise, the kidney showed normal structure that characterized by the cortex with normal renal corpuscles, formed from proximal convoluted tubules, distal convoluted tubules and glomeruli enveloped by Bowman's capsule (Figure 2).

Conversely, the liver sections from MSG-treated displayed pronounced pathological changes, characterized by vacuolar degeneration in hepatic cells with fibrous tissue proliferation and congestion in portal artery as well as necrotic changes in hepatic cells were detected (Figures 3,4). While, the kidney in this group showed necrosis in the epithelial lining of the renal tubules and in glomerular cells, with dilation in glomerular capillaries, besides, renal casts inside the lumen of the renal tubules, and inflammatory edema surrounded the blood vessel in renal cortex, other rats showed hypercellularity in the glomerular tissues with congestion in glomerular capillaries and severe dilation in the lumen of renal tubules with flattening in lining epithelium (Figures 5,6,7).

In the group treated with MSG+PJ, the liver displayed necrosis in few cells, with apparently normal in remaining of hepatic cells (Figure 8). Similarly, the kidney in this group showed mild degenerative and necrotic changes in renal tubules (Figure 9).

In the group treated with MSG+BP, the liver appeared apparently normal with normal arrangement of hepatocytes in most rats, other rats showed congestion in the central vein with regeneration in the hepatic cells characterized by nuclear division inside the cells (Figures 10,11). Similarly, the kidney in this group showed mild to moderate degenerative changes in epithelial lining of the renal tubules (Figure 12).

In the group treated with MSG+PJ+BP, the liver showed congestion in the blood vessels (Figure 13). While the kidney in this group showed congestion in all glomerular capillaries and moderate degenerative and renal casts (Figure 14).

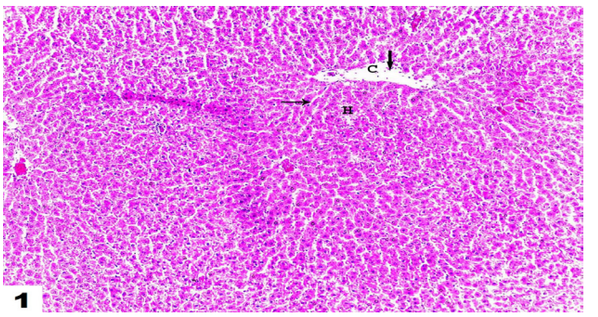

Fig. 1: A photomicrograph of liver section of the normal group, showing normal structure of hepatic lobules with normal structure of hepatic cells (H (thin black arrow)) arranged in linear cords between a blood sinusoids, and a central vein (C (thick black arrow)). (H&E., x 150).

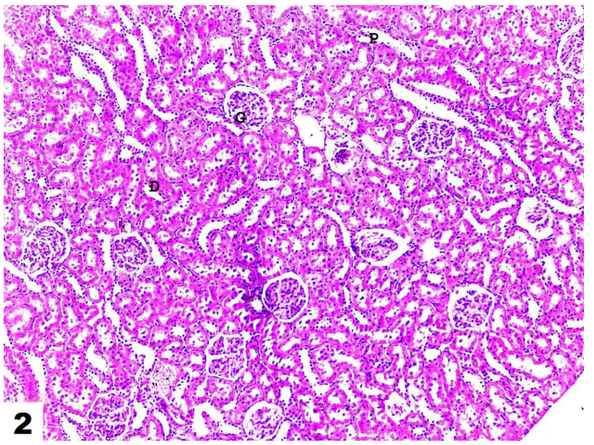

Fig. 2: A photomicrograph of renal section of the normal group showing normal structure of the kidney characterized by the cortex with normal renal corpuscles, formed from proximal convoluted tubules (P), distal convoluted tubules (D) and glomeruli enveloped by Bowman's capsule (G) (H&E., x 150).

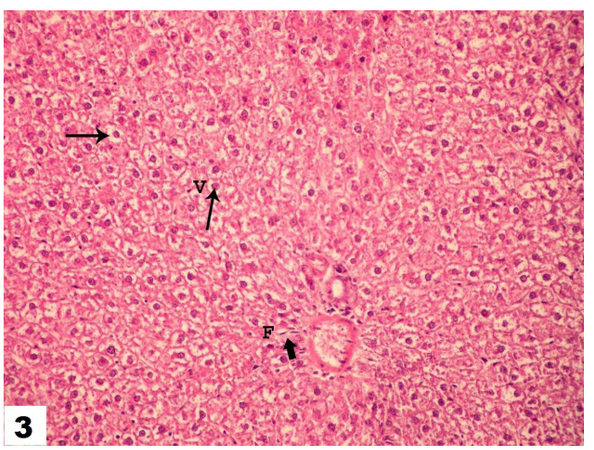

Fig. 3: A photomicrograph of liver section of the MSG-treated group, showing vacuolar degeneration in hepatic cells (V (thin black arrow)), with fibrous tissue proliferation (F (thick black arrow)) and congestion in portal artery. (H&E., x 200).

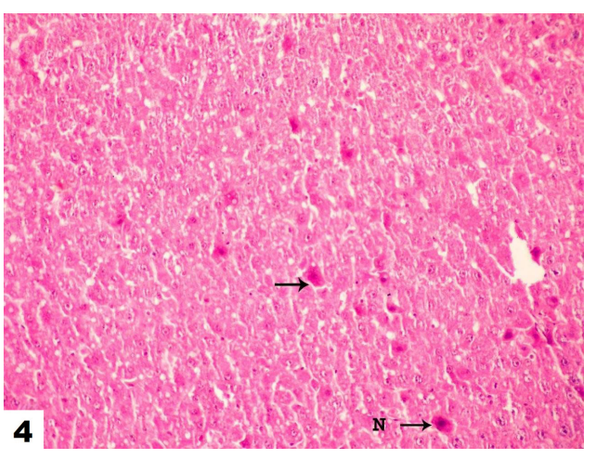

Fig. 4: A photomicrograph of liver section of rats in MSG-treated group showing necrotic changes (N (black arrows)) in hepatic cells. (H&E., x 150).

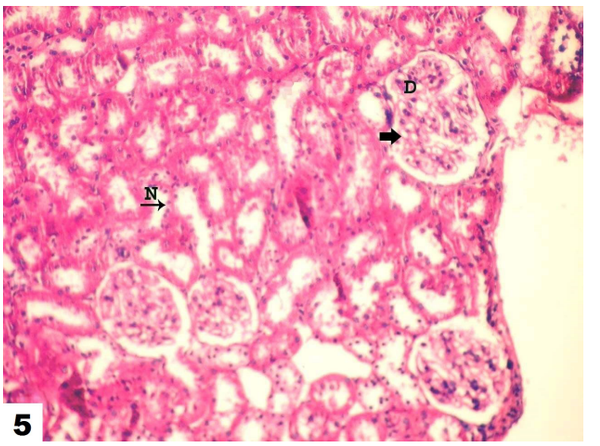

Fig. 5: A photomicrograph of renal section of the MSG-treated group showing necrosis (N (thin black arrow)) in the epithelial lining of the renal tubules and in glomerular cells, with dilation (D (thick black arrow)) in glomerular capillaries. (H&E., x 200).

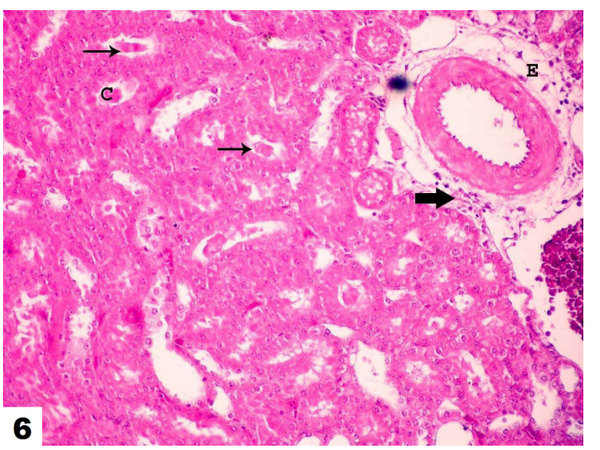

Fig. 6: A photomicrograph of renal section of the MSG-treated group showing renal casts (C (thin black arrow)) inside the lumen of the renal tubules, and inflammatory edema (E (thick black arrow)) surrounded the blood vessel in renal cortex. (H&E., x 200).

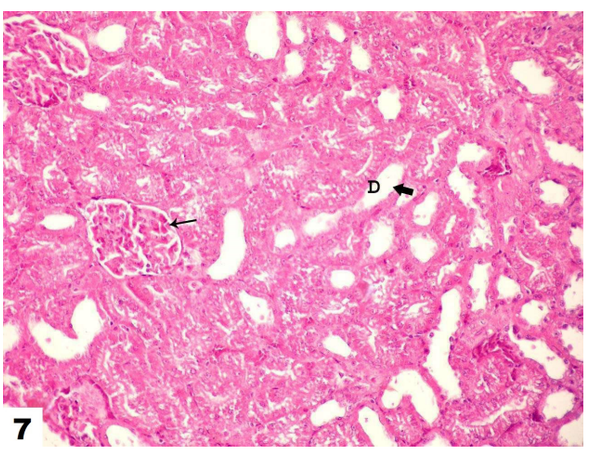

Fig. 7: A photomicrograph of renal section of the MSG-treated group showing hypercellularity (thin black arrow) in the glomerular tissues with congestion in glomerular capillaries and severe dilation in the lumen of renal tubules with flattening in lining epithelium (D (thick black arrow)). (H&E., x 150).

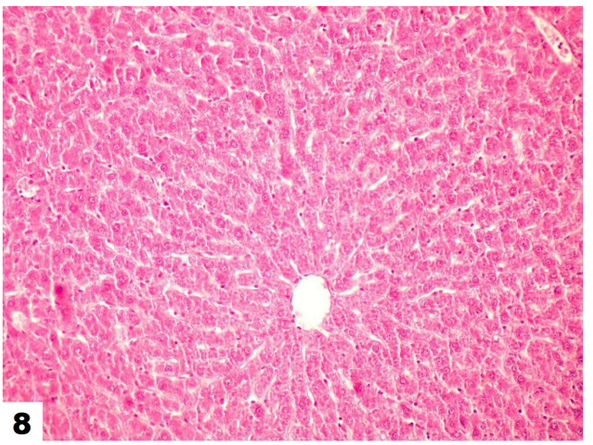

Fig. 8: A photomicrograph of liver section of the MSG+PJ treated group showing necrosis in few cells, with apparently normal in remaining of hepatic cells. (H&E., x 200).

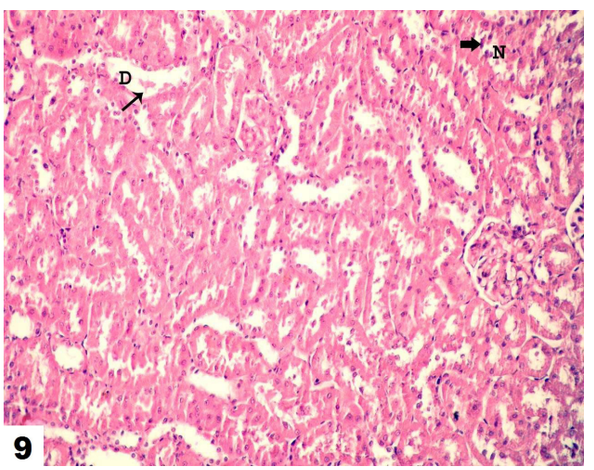

Fig. 9: A photomicrograph of renal section of the MSG+PJ treated group showing mild degenerative (D (thin black arrow)) and necrotic changes (N (thick black arrow)) in renal tubules (H&E., x 150).

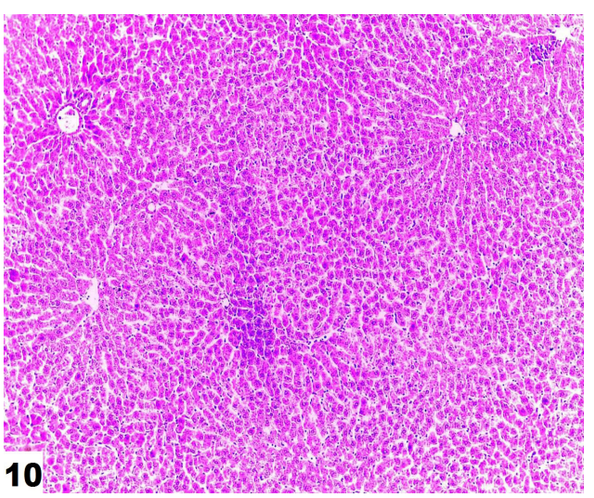

Fig. 10: A photomicrograph of liver section of the MSG+BP treated group is apparently normal with normal arrangement of hepatocytes (H&E., x 80).

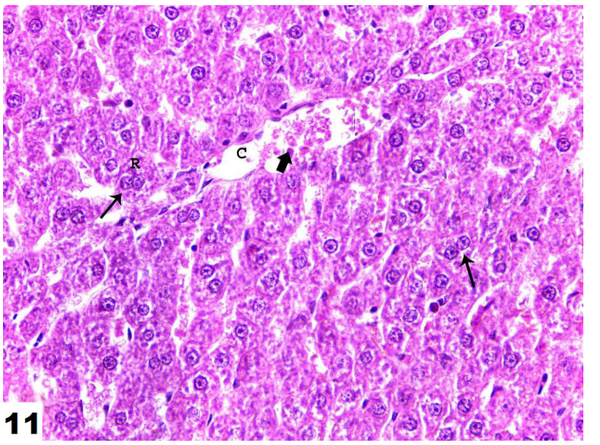

Fig. 11: A photomicrograph of liver section of the MSG+BP treated group showing congestion (C (thick black arrow)) in the central vein with regeneration (R (thin black arrows)) in the hepatic cells characterized by nuclear division inside the cells. (H&E., x 200).

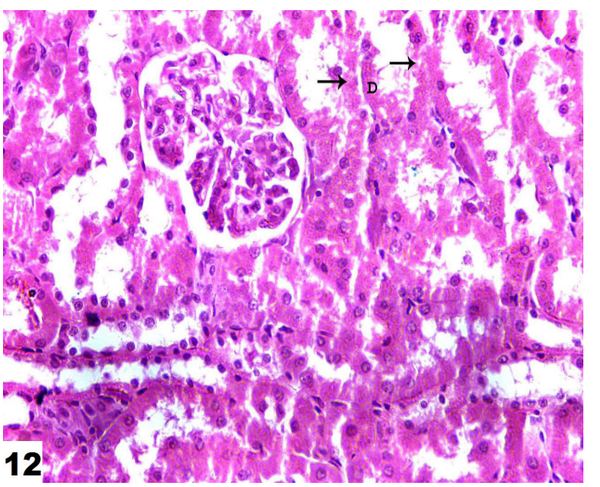

Fig. 12: A photomicrograph of renal section of the MSG+BP treated group showing mild to moderate degenerative changes (D (thin black arrows)) in epithelial lining of the renal tubules. (H&E., x 200).

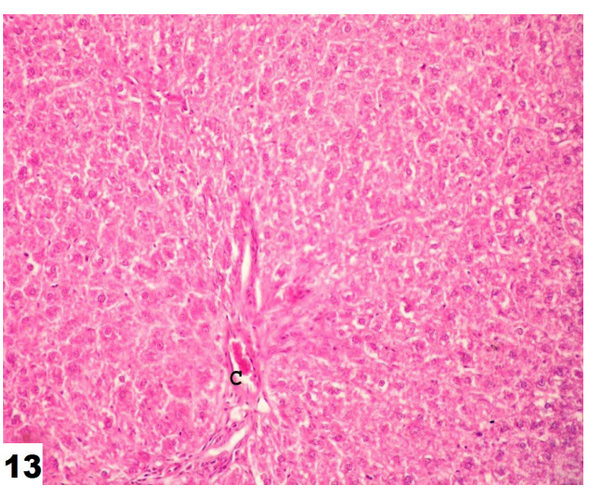

Fig. 13: A photomicrograph of liver section of the MSG+PJ+BP treated group showing congestion (C) in the blood vessels (H&E., x 150).

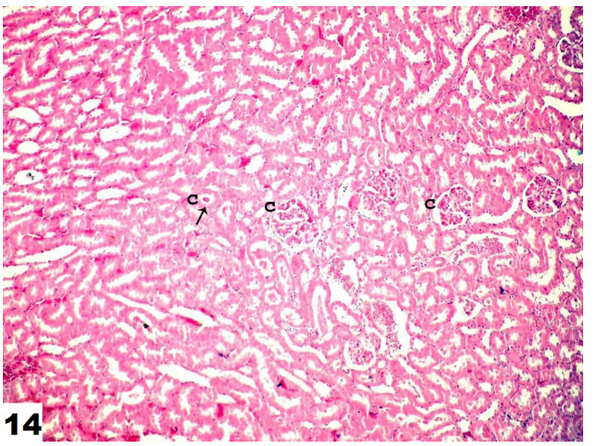

Fig. 14: A photomicrograph of renal section of the MSG+PJ+BP treated group showing congestion (C) in all glomerular capillaries and moderate degenerative and renal casts (C (thin black arrow)). (H&E., x 80).

Table 1: Effect of oral administration of daily doses of PJ (4ml/kg b.w.), BP (200mg/kg b. w.) and (PJ at a dose of 4ml/kg b.w. + BP at a dose of 200mg/kg b.w.) for 6 weeks, after treating orally with MSG (2.4g/kg b.w. daily for 4 weeks) on serum levels of AST, ALT, albumin and total protein.

Group	Normal (Mean ± S.D)	MSG (Mean ± S.D)	MSG+PJ (Mean ± S.D)	MSG+BP (Mean ± S.D)	MSG+PJ+BP (Mean ± S.D)
AST (U/ml)	109.5 ±16.46	220.4^{+X} ±17.8	134.2^{-Y} ±12.07	144.4^{-Y} ±25.5	118.7^{-Y} ±12.3
ALT (U/ml)	44.35 ±5.67	91.78^{+X} ±8.32	49.9^{-Y} ±6.78	55.09^{-Y} ±7.45	49.4^{-Y} ±7.92
Albumin (g/dl)	3.50 ±0.14	2.67^{-X} ±0.19	3.32^{+Y} ±0.22	3.23^{+Y} ±0.24	3.36^{+Y} ±0.15
Total protein (g/dl)	6.49 ±0.29	5.45^{-X} ±0.58	6.662^{+Y} ±0.29	6.22^{+Y} ±0.24	6.64^{+Y} ±0.26

All results are expressed as mean ± S.D. of 6 rats for each group.

+X = significant increased relative to normal at $p<0.05$.

-X = significant decreased relative to normal at $p<0.05$.

+Y = significant increased relative to MSG at $p<0.05$.

-Y =significant decreased relative to MSG at $p<0.05$.

Table 2: Effect of oral administration of daily doses of PJ (4ml/kg b.w.), BP (200mg/kg b. w.) and (PJ at a dose of 4ml/kg b.w. + BP at a dose of 200mg/kg b.w.) for 6 weeks, after treating orally with MSG (2.4g/kg b.w. daily for 4 weeks) on serum levels of TC, TGs, HDL, LDL and VLDL.

Group	Normal (Mean±S.D)	MSG (Mean ± S.D)	MSG+PJ (Mean ± S.D)	MSG+BP (Mean ± S.D)	MSG+PJ+BP (Mean ± S.D)
TC (mg/dl)	79.89± 3.04	99.28^{+X} ± 8.57	84.34^{-Y} ± 9.51	84.05^{-Y} ± 3.99	83.32^{-Y} ±5.19
TGs (mg/dl)	94.7± 5.54	163.4^{+X} ± 25.91	107.6^{-Y} ± 19.92	111.1^{-Y} ± 4.94	112.4^{-Y} ±11.5
HDL (mg/dl)	52.33± 1.33	44.85^{-X} ± 2.23	52.87^{+Y} ± 4.41	50.88^{+Y} ± 2.47	53.06^{+Y} ±4.78
LDL (mg/dl)	8.66± 2.38	20.88^{+X} ± 1.22	9.94^{-Y} ± 1.23	10.96^{-Y} ± 1.14	7.74^{-Y} ±1.03
VLDL (mg/dl)	18.92±1.49	32.78^{+X} ±6.08	21.52^{-Y} ± 3.34	22.21^{-Y} ± 1.27	22.5^{-Y} ±2.41

All results are expressed as mean ± S.D. of 6 rats for each group.

+X = significant increased relative to normal at $p<0.05$.

-X = significant decreased relative to normal at $p<0.05$.

+Y = significant increased relative to MSG at $p<0.05$.

-Y =significant decreased relative to MSG at $p<0.05$.

Table 3: Effect of oral administration of daily doses of PJ (4ml/kg b.w.), BP (200mg/kg b. w.) and (PJ at a dose of 4ml/kg b.w. + BP at a dose of 200mg/kg b.w.) for 6 weeks, after treating orally with MSG (2.4g/kg b.w. daily for 4 weeks) on serum levels of Creatinine, Urea and Uric acid.

Group	Normal (Mean ± S.D)	MSG (Mean ± S.D)	MSG+PJ (Mean ± S.D)	MSG+BP (Mean ± S.D)	MSG+PJ+BP (Mean ± S.D)
Creatinine(mg/dl)	0.72±0.098	1.38^{+X} ± 0.15	0.77^{-Y} ±0.06	0.8^{-Y} ±0.096	0.74^{-Y} ± 0.12
Urea (mg/dl)	45.48±3.94	98.82^{+X} ±6.19	51.12^{-Y} ± 6.66	53.2^{-Y} ± 5.39	49.27^{-Y} ±5.21
Uric acid (mg/dl)	1.85±0.17	3.91^{+X} ±0.34	2.15^{-Y} ±0.42	2.26^{-Y} ± 0.43	1.92^{-Y} ±0.27

All results are expressed as mean ± S.D. of 6 rats for each group.

+X = significant increased relative to normal at $p<0.05$.

-X = significant decreased relative to normal at $p<0.05$.

+Y = significant increased relative to MSG at $p<0.05$.

-Y =significant decreased relative to MSG at $p<0.05$.

Table 4: Effect of oral administration of daily doses of PJ (4ml/kg b.w.), BP (200mg/kg b.w.) and (PJ at a dose of 4ml/kg b.w. + BP at a dose of 200mg/kg b.w.) daily for 6 weeks of treatment, after treating orally with MSG (2.4g/kg b.w. daily for 4 weeks) on Hepatic and Renal TAC and MDA levels.

Group	Normal (Mean ± S.D)	MSG (Mean ± S.D)	MSG+PJ (Mean ± S.D)	MSG+BP (Mean ± S.D)	MSG+PJ+BP (Mean ± S.D)
Hepatic-TAC (mM/L)	94.21±6.14	56.41^{-X} ±8.01	86.68^{+Y}±6.83	83.77^{+Y} ± 7.32	87.64^{+Y} ±6.77
Renal-TAC (mM/L)	79.39±5.41	44.54^{-X} ±5.65	70.20^{+Y} ± 6.57	68.51^{+Y} ± 8.18	69.84^{+Y} ±7.97
Hepaic-MDA (nmol/g.tissue)	32.25± 4.51	65.27^{+X} ±5.74	37.75^{-Y} ± 5.82	39.79^{-Y} ± 5.97	37.94^{-Y} ±6.28
Renal-MDA (nmol/g.tissue)	37.29± 3.14	77.61^{+X} ±4.96	41.07^{-Y} ± 6.37	44.49^{-Y} ± 7.20	42.37^{-Y} ±6.97

All results are expressed as mean ± S.D. of 6 rats for each group.

+X = significant increased relative to normal at $p<0.05$.

-X = significant decreased relative to normal at $p<0.05$.

+Y = significant increased relative to MSG at $p<0.05$.

-Y =significant decreased relative to MSG at $p<0.05$.

DISCUSSION

Generally, the present study showed that the daily consuming of MSG may result in significant disorders in the hepatic and renal biochemical parameters, as well as histological harmful abnormalities. On the other hand, administration of PJ and/or BP most likely ameliorated the MSG-induced pathological changes in the hepatic and renal tissues.

The current study revealed significant increase in the serum AST and ALT enzyme activities, however total protein and albumin recorded significant decrease after MSG administration, supporting the evidence of[14] who demonstrated that MSG causes destruction of hepatocytes. Also, the present results run in full agreement with[15] who reported that in the hepatocytes, sodium moiety could dissociate easily from MSG producing free glutamate. Thus, increasing the overloading chance of toxic ammonium ion that damage the hepatocytes, or included in the reactions of the urea cycle that is mainly exhausting kidneys. Moreover, according to[16], the elevation of AST and ALT levels can be attributed to oxidative damage caused by MSG, leading to changes in the integrity of hepatocyte membranes, which results in the leakage of AST and ALT. Besides, significant decrease in serum albumin and total protein is in full agreement with[10]. This might be due to the increase in the protein degradation rate or disturbances in protein synthesis as MSG induces hepatic histologically and functionally alterations[17,18]. However, our data showed a pronounced decrease in the activities of serum AST and ALT and a significant increase in albumin and total protein after PJ supplementation, as it can modulate and regenerate the disturbed hepatic structural organization. This is in full agreement with[19] who used PJ against carbon tetrachloride hepatotoxicity. Additionally, this ameliorative effect of PJ is in agreement with[11] who reported that *Punica granatum* ameliorative effects against toluene hepatotoxicity relates to its considerable free radical scavenging ability. According to[20] pomegranate has been suggested to play ameliorating role against hepatotoxicity due to its high content of phenolic compounds, ellagic tannins, flavonoids and anthocyanins, that have strong antioxidant capacities. Moreover, albumin and total protein improvements might be due to acceleration of the regeneration and recovery of damaged hepatocytes. Above of all, the current results showed that BP administration resulted in pronounced

decrease in the serum activities of AST and ALT and significant increase in albumin and total protein, these results are in agreement with[21] who investigated the ameliorating effect of BP against thioacetamide toxicity, this mainly relates to the antioxidant activities of phenolic compounds present in BP, that help in hepatocytes improvement and regeneration throughout inhibition of cytochrome P450 aromatase activity[22]. Furthermore, our recorded results are in accordance with[23] who proved the positive therapeutic effect of BP against fluvastatin-induced hepatitis in rats.

In addition, the current results revealed that MSG-administration resulted in impairment in liver markers including lipid profile alterations that manifested by significant increasing in TC, TGs, VLDL and LDL levels as well as significant reduction in HDL level, these results run in the same line with[10,24]. This might relate to plasma membrane lipids peroxidation (LPO) or to free fatty acids motivation out of the adipose tissues to the bloodstream[25,26]. Also MSG could increase the activity of the rate-limiting enzyme in the cholesterol biosynthesis (3-hydroxyl-3-methylglutrayl-Coenzyme A reductase) which resulted in increasing in cholesterol synthesis and reduction in TC and TGs metabolism (i.e., increasing their serum levels), shifting the glucose metabolism towards lipogenesis[27]. Also MSG induces catabolism of the hepatic lipid, via oxidative genes up regulation, activating bile acid pathway genes including cholesterol-7-α hydroxylase as well as key regulatory enzyme[28]. On the other hand, oral administration of PJ resulted in significant reductions in TC, TGs, LDL and VLDL, while HDL level was increased, this in agreement with[29] who reported that PJ consumption results in significant reduction in accumulation of cholesterol. This might relate to the high ability of PJ in scavenging free radicals[30,31]. Also these ameliorative effects of PJ are in accordance with those obtained by[32]. Furthermore, BP administration resulted in well improvements in the lipid profile parameters including reduction in serum TC, TGs, LDL and VLDL, however serum HDL recorded a significant increase. These data are in agreement with those that reported by[33] who proved the ability of BP to restore the normal hepatic functions damaged by propionic acid depending upon its potentially effective antioxidant components.

Above all, the results of this study indicated that the hepatic antioxidant abilities are changed after MSG administration, manifested by a inhibition in its TAC and significant high level of MDA. This is in accordance with[28,34] who reported that reactive oxygen species (ROS), induced by MSG, attack polyunsaturated fatty acids initiating LPO inside cells, as glutamate could not transport across plasma membranes and accumulated intracellularly, altering the cellular redox potential resulting in aldehyde products formation, such as MDA, these aldehyde products can diffuse from their destinations of cause to achieve far off extracellular and intracellular targets resulting in cell membrane disruption and cellular functions disorders that highly affect the cell production of the antioxidant enzymes leading to reduction in TAC[35]. In addition, this reduction in the hepatic-TAC level is similar to[36] who reported that MSG induces significant reductions in the levels of some antioxidant markers (TAC, Catalase, total glutathione content, reduced glutathione). However, the present data revealed that, MSG+PJ treated rats showed a significant decrease in hepatic MDA levels and a significant increase in hepatic TAC levels. we relate this PJ positive ameliorative effects to its antioxidant as well as its anti-inflammatory properties depending upon its chemical components including punicalagin, the main ellagic tannin which is responsible for the PJ antioxidant efficiency by increasing C-glutamyl cysteine synthetase, the critical enzyme in the GSH synthesis, and increasing serum paraoxonase activity, which may protect hepatic tissue against LPO[37-39]. According to[40] PJ contains vitamin C that is well known with its antioxidant activities, that might share in hepatic amelioration. Additionally, our recorded results showed that BP could reduce the hepatic MDA and elevate the hepatic TAC, relative to MSG treated rats, this ameliorative effects of BP against hepatic toxicity is in agreement with[21]. It is worth to mention that all these hepatic ameliorations, after PJ and BP administration relative to the MSG treated rats, are proved and supported by the significant histological improvements observed in the liver of PJ and BP supplemented rats.

Moreover, our results showed significant increase in the serum creatinine, urea and uric acid following MSG administration, this in consistent with the findings of[28,41]. As a result of increasing the deamination process, due to MSG severe consuming, and its detoxification in the liver, the rate of urea production increases that is excreted mainly by the kidneys leading to its exhausting followed by renal diseases. explained[42] that these nephrotoxic effects might be due to ROS formation in the kidneys leading to cellular and functional damage. Additionally, our data revealed that MSG resulted in inhibition in renal TAC and significant high levels of its MDA, this runs in the same line with[43] who demonstrated that, MSG consuming causes elevation of ROS levels resulting in a reduction in antioxidant enzymes activities (i.e., significant reduction in TAC levels) while an increase in oxidative stress and LPO (i.e., MDA), giving rise to kidneys structural damage. It is worth to mention that, glutamate receptors are distributed in peripheral organs including liver and kidneys[44]. In our study, overstimulation of these hepatic and renal receptors by glutamate could lead to ROS production and LPO motivation, consequently hepatic and renal oxidative damage and functional impairments.

In regard to the MSG+PJ treated rats, there is significant decrease in serum creatinine, urea and uric acid levels relative to MSG-treated ones, this is in accordance with[45], who proved the ameliorative effects of PJ against liver and kidney dysfunctions against copper oxide nanoparticles. Additionally our recorded renal ameliorations by PJ run in the same line with[46] who proved that pomegranate

has the ability to ameliorate the renal histopathological and biochemical abnormalities induced by cyclosporine. Also this PJ renal amelioration effects against MSG nephrotoxicity, are similar to its strong antioxidant effects against nicotine[47]. As the oxidative stress caused by MSG has a significant role in the occurrence of renal damage, polyphenols exist in PJ were suggested to play a critical antioxidant action against this damage[22,23]. In addition, we can relate the reduction in uric acid after PJ supplementation to the ameliorations in the overall of renal functions as uric acid is excreted mainly by the kidneys. Besides that, the current data revealed that, MSG+PJ treated rats showed a significant decrease in renal MDA and a significant increase in renal TAC levels, comparing to MSG-administered ones, we suggest this amelioration effects of PJ to its antioxidant as well as its anti-inflammatory properties. According to our results, MSG produced severe renal toxic effects, nevertheless these harmful effects could be treated by means of natural and available potentially effective antioxidant like BP as it could increase antioxidant capabilities of some tissues including the liver and kidneys of model animals[21]. In addition, our data indicated that BP can significantly reduce renal MDA levels and increase TAC level. BP, being an anti-lipoperoxidant agent, it inhibits the LPO (i.e., reduction in MDA). BP antioxidant activities are attributed to its structure, depending on its high content of the bioflavonoid and polyphenolic compounds[48]. All these amelioration effects of PJ and BP against MSG renal toxicity are proved and supported by our histopathological finding which revealed that PJ and BP could ameliorate the renal histological abnormalities resulted from MSG administration.

CONCLUSION

In conclusion, our findings indicate that MSG induced hepatic and renal toxicity, as evidenced by elevated levels of serum hepatic enzymes (AST, ALT), decrease in albumin and total protein, disturbances in the serum lipid profile, manifested by increasing in TC, TGs, LDL and VLDL, a significant reduction in serum HDL. besides elevations in serum creatinine, urea and uric acid. Additionally, MSG resulted in hepatic and renal oxidative stress including significant reduction in TAC and significant increasing in their MDA levels. On the other hand, PJ and BP, either each one separately or both together, expressed antioxidant and ameliorative effects against MSG hepatic and renal toxicities. So, based on our findings, we recommend reducing daily MSG consumption as much as possible. Additionally, our results suggest incorporating PJ and BP into our daily diet as natural, potentially effective antioxidants.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

التأثيرات التحسينية لعصيرالرمان وحبوب لقاح نحل العسل ضد سُمية الكبد والكُلي المستحثة بواسطة جلوتامات أحادية الصوديوم في ذكور الجرذان البيضاء البالغة

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[١]قسم علم الحيوان، كلية العلوم، [٢]قسم الباثولوجيا الإكلينيكية، كلية الطب البيطري، جامعة جنوب الوادي، قنا، مصر

الهدف من الدراسة: هدفت هذه الدراسة إلي توضيح التأثيرات التحسينية ل عصير الرمان ((PJ وحبوب لقاح نحل العسل (BP) ضد سُمية الكبد والكُلى الناجمة عن جلوتامات أحادية الصوديوم (MSG) في ذكور الجرذان البيضاء البالغة.

المواد والطرق: لقد تم استخدام ٣٠ من ذكور الجرذان البيضاء البالغة، تراوحت أوزانهم من ١٩٠-٢١٠ جم، وتم تقسيمهم عشوائيًا إلي ٥ مجموعات بكل مجموعة ٦ جرذان: المجموعة الأولي (مجموعة طبيعية) وفيها عُولجت الجرذان فمويًا ب ماء مقطر لمدة ١٠ أسابيع، وعُولجت باقي المجموعات فمويًا ب جلوتامات أحادية الصوديوم مرة واحدة يوميًا عند جرعة (٢,٤جرام/كجم من وزن الجسم) لمدة ٤ أسابيع. ثم بعد ذلك؛ عُولجت المجموعة الثالثة فمويًا ب عصير الرمان مرة واحدة يوميًا عند جرعة (٤ مللي/كجم من وزن الجسم) لمدة ٦ أسابيع، أما المجموعة الرابعة فقد عُولجت فمويًا ب حبوب لقاح نحل العسل مرة واحدة يوميًا عند جرعة (٢٠٠مللي/كجم من وزن الجسم) لمدة ٦ أسابيع، وأخيرًا عُولجت المجموعة الخامسة فمويًا ب (عصير الرمان و حبوب لقاح نحل العسل) معًا مرة واحدة يوميًا لمدة ٦ أسابيع. بعد مرور ٢٤ ساعة من حقن آخر جرعة؛ تم تجميع عينات الدم من كل المجموعات لعمل التحاليل البيو كيميائية الخاصة ب وظائف الكبد (أسبراتيت أمينوترنسفيريز (AST)، الألانين أمينوترنسفيريز (ALT)، الألبومين والبروتين الكلي) ووظائف الكُلى (اليوريا، الكرياتينين وحمض اليوريك) وكذلك فحص مستويات الكولسيتيرول والدهون بالدم (الكولسيتيرول الكلي (TC)، الدهون الثلاثية ((TGs، الكولسيتيرول منخفض الكثافة ((LDL، الكولسيتيرول ذو الكثافة المنخفضة جدا((VLDL، الكولسيتيرول مرتفع الكثافة ((HDL. ثم بعد ذلك تم تخدير الجرذان وتشريحها للحصول علي الكبد والكُلي لعمل التحاليل البيو كيميائية وكذلك لإجراء الفحوصات النسيجية لهما.

النتائج: لقد أظهرت النتائج ارتفاعًا ملحوظًا في مستويات (أسبراتيت أمينوترنسفيريز والألانين أمينوترنسفيريز) وكذلك انخفاضًا ملحوظًا في مستويات (الألبومين والبروتين الكلي) عند مستوي($p<٠,٠٥$) . بالاضافة إلي ملاحظة ارتفاعًا معنويًا في مستويات (اليوريا والكرياتينين وحمض اليوريك) عند مستوي (($p<٠,٠٥$. وأيضا أظهرت النتائج ارتفاعًا معنويًا في مستويات الكولسيتيرول الكلي، الدهون الثلاثية، الكولسيتيرول منخفض الكثافة، الكولسيتيرول ذو الكثافة المنخفضة جدًا، بجانب انخفاضًا ملحوظًا في مستوى الكولسيتيرول مرتفع الكثافة عند مستوي (($p<٠,٠٥$ في المجموعة الثانية التي حُقنت ب الجلوتامات أحادية الصوديوم بالمقارنة ب المجموعة الطبيعية. ومن ناحية أخرى تسببت الجلوتامات أحادية الصوديوم في زيادة معنوية ملحوظة في مستوي ثنائي ألدهيد المالون (MDA) وانخفاضًا معنويًا ملحوظًا في مستوى إجمال القدرة المضادة للأكسدة (TAC) في أنسجة الكبد والكُلى مقارنةً بالمجموعة الطبيعية، عند مستوي (($p<٠,٠٥$. ومن الجدير بالذكر، فقد أظهرت النتائج تدهورًا حادًا في أنسجة الكبد والكُلى للجرذان المحقونة ب الجلوتامات أحادية الصوديوم، مقارنةً بالمجموعة الطبيعية. علي الجانب الاخر، فقد أوضحت النتائج تحسنًا معنويًا في كل هذه التغيرات الدموية والنسيجية بعد استخدام كلاً من عصير الرمان وحبوب لقاح نحل العسل، كل علي حدي أو كليهما معًا.

الاستنتاج: أكدت هذه الدراسة مدي سُمية فرط استخدام الجلوتامات أحادية الصوديوم علي الكبد والكُلى في ذكور الجرذان البيضاء، مشيرةً إلي مدي خطورة الاستخدام المفرط لهذا المضاف الغذائي، سواء بكميات كبيرة أو حتي بكميات قليلة بشكل يومي دائم، علي جسم الانسان أيضًا، لذا نوصي بالتقليل من استخدام هذا المضاف الغذائي في حياتنا اليومية بقدر المستطاع. ومما هو جدير بالذكر أيضًا؛ فقد أثبتت هذه الدراسة مدي كفاءة وفاعلية عصير الرمان و حبوب لقاح نحل العسل كمضادات للأكسدة من مصادر طبيعية ضد سُمية تلك المضاف الغذائي.