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# Possible Protective Effects Of Atorvastatin And Nigella Sativa Oil On The Kidney Of Adult Rats Exposed To Monosodium Glutamate

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**ABSTRACT**

**Background:** Monosodium glutamate (MSG) is a commonly used food additive. Many experimental animal models have recorded possible damages in some organs caused by MSG effects.

**Objective:** This study aimed to assess and compare the protective effects of Nigella sativa (N.S)/atorvastatin on the renal tissue on exposure to MSG.

**Materials and Methods:** Fourty adult male albino rats were randomly divided into four equal groups (n = 10/each): 1 (Control); 2 (MSG 35 mg/kg b.w); 3 (MSG + Atorvastatin 5 mg/kg/d); and 4 (MSG + Nigella sativa oil 400 mg/kg/d). At the end of the experiment period, rats were sacrificed and blood samples were collected for kidney functionsand serum SOD in kidney,then kidney was removed and prepared for histopathological, immunohistochemistry examination and tissue homogenate for assessments of renal malondialdehyde (MDA).

**Results:** MSG increased the serum level of creatinine, urea, uric acid, MDA, and renal Caspase-3 expression, while the renal expression of SOD expression was decreased in comparison to the control group. However, Co-administration of atorvastatin/nigella sativato MSG reduced serum creatinine, urea, uric acid, MDA, expression of Caspase-3and increased SOD in referral to the MSG group.

**Conclusion:** This study suggests that the nigella sativa and atorvastatin, are capable of ameliorating the hazardous renal effects of MSG via their antioxidant and anti-apoptotic actions.

**Keywords:** Monosodium glutamate, Food Additives, Nephrotoxicity, Nigella Sativa; Atorvastatin.

## INTRODUCTION

Food additives are substances added to food toimprove its taste, appearance, or other qualities, preserve its flavor and are inevitable in packaged food**(Wu et al., 2021).**Monosodium glutamate (MSG) is a common food additive used to improve palatability, especially in industrially processed foods**(Nahok et al., 2021).**

Using MSG as a food additive was reported as safe for human according to the last FDA reports **(Shukry et al., 2020).**But it is still disputed as many studies found that intake of MSG in food led to human diseases as metabolic syndrome, obesity, hypertension,additionally damages to vital organs as liver, brain, thyroid, and kidney**(Elbassuoni et al., 2018, Mekkawy et al., 2020, Nahok et al., 2019).**Chronic exposure to MSG induced severe nephrotoxicity associated with cellular dysfunctions**(Sharma et al., 2014).** Also, glomerular infiltrationby inflammatory cells in the renal cortex were detected in MSG exposed rats**(Dixit et al., 2014).**

The disproportion between increased free radicals' production and cellular antioxidant system is a major cause of MSG-mediated hepatorenal diseases**(Eid et al., 2019).**Also, the imbalance between cellular free radical production/elimination (as reactive oxygen species (ROS)) initiates an oxidative stress state that causes harmful effects to various body systems**(Charlton et al., 2021).**Moreover that, in MSG-exposed rats, there were deficiency inthe antioxidant defense system confirmed bydecreased levels of antioxidant enzymes and increase dlipid peroxidation**(Sharma, 2015).**

Antioxidants are scavengers for free radicals which ameliorate the hazardous effects of ROS**(Koohpeyma et al., 2021).**Thus, it seems that the use of antioxidants may alleviate these changes induced by MSG. Nigella sativa (black seeds) is a common natural herb usually has a broad use in traditional medicine due to its antiinflammatory, antioxidative and tissue-protective properties**(Mekkawy et al., 2020).**

Statins (e.g: atorvastatin) are drugs that lower the cholesterol level in the blood, acting as HMG Co-A reductase inhibitors (rate-limiting enzyme in cholesterol biosynthesis). But they possess other beneficial pleiotropic effects, as antioxidant, immunomodulatory, and anti-inflammatory properties**(Mounier et al., 2021).** Low dose of atorvastatin was effective in the hypercholesterolemia management as well as its antioxidant and anti-inflammatory actions**(Gadallah and Hanan, 2020).**On the other hand, high-dose of atorvastatin was found to cause many complications as nephrotoxicity and testicular injury**(Hashem et al., 2015).**

Also, to our knowledge few studies are present to assess the role of atorvastatin in alleviating the harmful effects of MSG on the kidney. So, the present study was designed to evaluate and compare the effectiveness of nigella sativa and atorvastatin on the kidney structure &functions on exposure to Monosodium glutamate toxicity.

## MATERIALS AND METHODS

### Chemicals

Monosodium glutamate and Nigella Sativa oil was purchased from the Local available market, and Atorvastatin 100 mg tablet were obtained from Egyptian International Pharmaceutical Industries Co (EIPCO) 10th of Ramadan City, Egypt. All other chemicals were obtained from the local market.

**Animals**

Forty adult male albino rats of 100-120 gm/weight were used in this study. The animals were obtained from animal house of veterinary serum & vaccine research institute (Abbasya, Cairo, Egypt). The rats were acclimatized for one week previous to the experiment. Rats were kept in cages in a suitable environment that was maintained under a 12-hour light/dark cycle, a temperature of 27°C (±3°C) and supplied with a standard rat diet with free access to tap water.

**Medical ethics approval**

Animal handling was approved by the medical ethical committee, Damietta Faculty of Medicine, Al Azhar University, Egypt (IRB0001267-21-06-009).

**Experimental animal design**

Rats were randomly divided into four groups: 1) Normal control group: each rat was fed a normal diet and equivalent volume of corn oil by oral gavage daily for two weeks 2) MSG group: each rat was given a dose of MSG (35 mg/kg/day), dissolved in saline by oral gavage for two weeks. This dose is a little more than acceptable daily dose intake of MSG (30 mg/kg/d) reported by the European Food Safety Authority3) MSG + Atorvastatin group: each rat was given a dose of MSG (35 mg/kg/day), dissolved in saline in addition to atorvastatindose (5 mg/kg/day) suspended in corn oil by oral gavage for 2 weeks. 4) MSG + Nigella sativa group: each rat was given a dose of MSG (35 mg/kg/day), dissolved in saline additionally to Nigella sativa oil in a dose of 400 mg/kg (corresponding to 0.46 ml/kg) by oral gavage for 2 weeks.

**Blood collection, Serum biochemical analyses**

At the end of the experiment, blood samples were obtained from the retro-orbital plexus, and then, serum was separated by centrifugation at 1200 g for 15 min. Serum was then collected and kept at 20 °C for biochemical analyses of serum urea (mg/dl), creatinine(mg/dl) and uric acid (mg/dl).Serum SOD (IU/ml) was measured with ELISA method according to the manufactureŕs recommendations.

**Hematoxylin and Eosin (H&E),Masson trichrome and immunohistochemistry**

The rats were sacrificed by cervical decapitation, kidney specimens were fixed in 10% formalin for 24 h. The obtained renal specimen were prepared and sectioned at 5 µm thickness and stained with, Hx.& E, Masson trichrome and immune stain for caspase3. The prepared slides were examined under light microscope (Raywild, Germany). The images were photographed & the percentage area density of collagen fibres & caspase 3 was measured using a digital camera with image-analyzing system (optimus v12) at 40X.

**Preparation of tissue homogenates**

An accurately weighted piece (0.3 g) of kidney specimen were homogenized according to (Huculeci et al., 2009)in ice phosphate buffer saline using a Teflon pestle connected to a homogenizer motor (25 strokes per minute at 1000 rpm), the kidney homogenate was diluted to yield 10 % (w/v) kidney homogenate, which was centrifuged at 13000 rpm for 30 min at 4 °C to remove cell debris and nuclei. The supernatant was used for biochemical determination of renal malondialdehyde (MDA).

**Statistics:** Data are represented as the mean ± SE. Data were analyzed by the two-tailed Student's -test and one-way ANOVA using the statistical software package SPSS for Windows

(Version 21.0; SPSS Inc., Chicago, IL, USA), followed by Duncan's post hoc test for multiple group comparison. Statistical significance was accepted at $P < 0.05$.

**RESULTS**

**Effects on kidney functions:**

Comparing to the normal rats, there were marked and significant increase in the level of serum creatinine, urea and uric acid in animals treated with MSG for 15 days, while a significant decrease in those levels in rats with daily administration nigella sativa / atorvastatin in combination with MSG for 15 days in comparison to MSG group. There was significant decrease in level of SOD in kidney in animals treated with MSG for 15 days in comparison to control group, while a significant decrease in its levels in rats treated with nigella sativa/ atorvastatin in combination with MSG for 15 days in comparison to MSG group (Table 1).

**Table 1: Assay of kidney functions and serum SOD:**

| Parameters / Groups | Creatinine (mg /dl) | Urea (mg /dl) | Uric acid (mg /dl) | SOD (IU/L) |
|---|---|---|---|---|
| Control | 0.41 ± 0.34 | 27.74 ± 5.14 | 4.34 ± 0.64 | 12.24±0.57 |
| MSG | 1.67 ± 0.28 [a] | 50.28 ± 6.17 [a] | 7.24 ± 0.67 [a] | 9.65±0.99 |
| MSG+ atorvastatin | 0.85 ± 0.34 [ab] | 33.71 ± 4.74 [a b] | 5.35 ± 0.74 [a b] | 11.04±0.51 [a b] |
| MSG+ Nigella | 0.74 ± 0.16 [a b] | 31.64 ± 2.52 [a b] | 5.15 ± 0.24 [a b] | 11.99 ± 0.43 [a b] |

Data are shown as mean ± SD.[a]Significantly different than control group at $p < 0.05$. [b]Significantly different than MSD exposed group at $p < 0.05$

**Effects on tissue levels of MDA, collagen & caspase 3 in the kidney:**

Tissue level of MDA, percentage area density of Collagen and Caspase 3of rats treated with MSG for 15 days was significantly increased in comparison to control group, while a significant reduction in those levels in rats treated with nigella sativa/atorvastatin in combination with MSG for 15 days in comparison to MSG group(Table 2).

**Table 2. Assay of tissue levels of MDA, Collagen and Caspase 3**

| Parameters / Groups | MDA (nmol/g tissue) | Percentage are of Collagen density % | Caspase 3 density ($mm^3$) |
|---|---|---|---|
| Control | 10.54 ± 1.27 | 5.45 ± 1.21 | 3.24 ± 0.62 |
| MSG | 25.34 ± 3.24 [a] | 10.21 ± 1.17 [a] | 11.82±2.27 [a] |
| MSG+ atorvastatin | 17.36 ± 2.41 [a b] | 8.34 ± 0.91 [a b] | 7.72±1.04 [a b] |
| MSG+ Nigella | 14.98 ± 2.04 [a b] | 7.87 ± 1.34 [a b] | 6.14±1.18 [a b] |

Data are shown as mean ± SD. [a]Significantly different than control group at $p < 0.05$.[b]Significantly different than MSD exposed group at $p < 0.05$.

**Light microscopic results**

**Hematoxylin and Eosin-stained sections results**

The rat kidney from Group I (control group): showed the renal cortex with normal histological appearance of renal corpuscles, Proximal convoluted tubules and distal convoluted tubules. Group II (MSG group):revealed rupture of one glomerulus, the other glomerulus showed widening of urinary space, increased vacuolization, damaged and vacuolated PCTs and DCTs with wider lumen. While, Group III, IV (MSG + Nigella Sativa/atorvastatin) treated rats: showed near normal structure, intact glomeruli with less widening of urinary space and intact glomerular membranes, PCTs, and DCTs. However, some damage in the glomeruli, PCT and DCTs were still observed in the atorvastatin group (Figure 1).

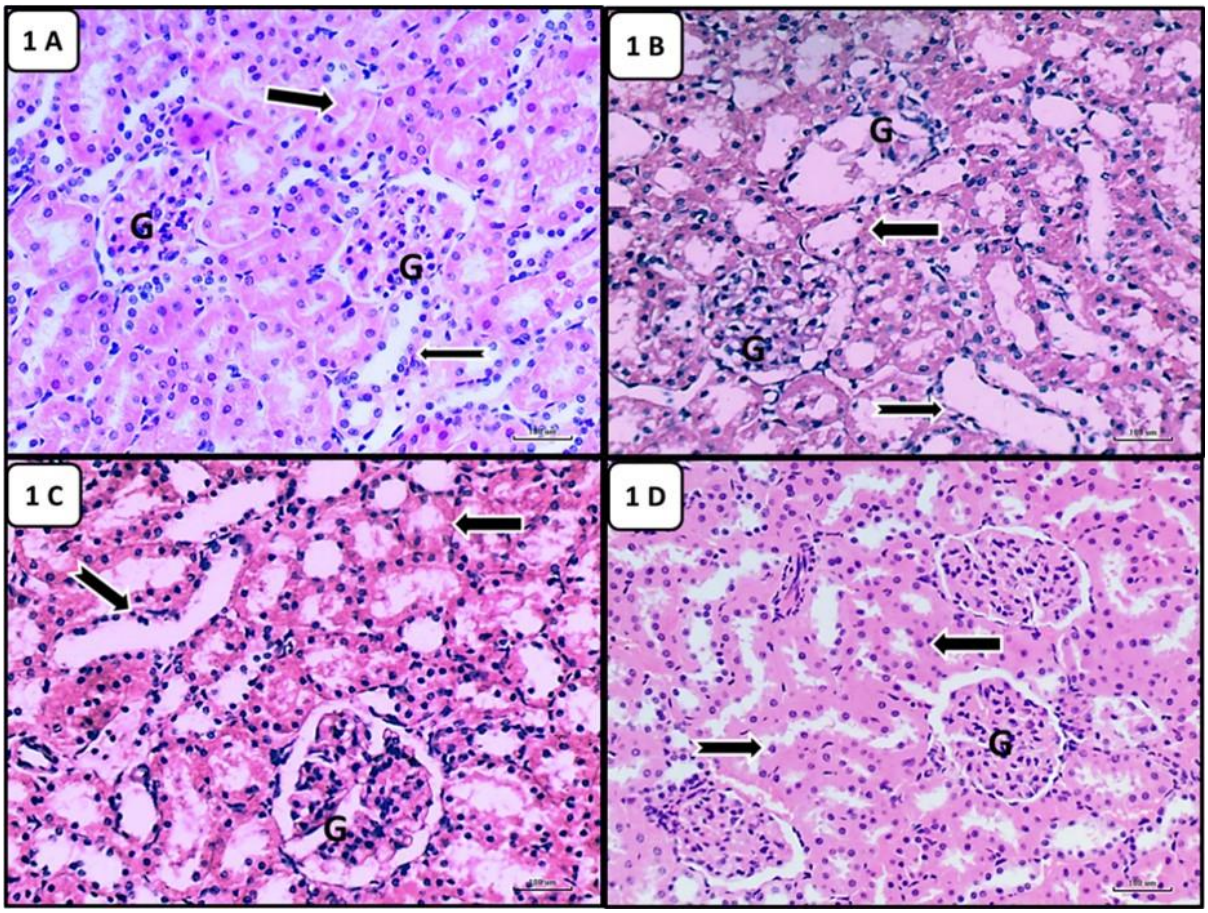


Figure (1). (A) The kidney from control rat group showed: normal histological appearance of renal corpuscles with its glomerulus (G) formed of capillary enclosed in a Bowman's capsule which is formed of inner visceral and outer parietal layers separated by urinary space. Proximal convoluted tubules (Thick arrow) with narrow lumen and lined with simple cubical epithelium. Less numerous distal convoluted tubules (thin notched arrow) with wide lumen and lined with simple cubical epithelium. (B) MSG treated rats showed marked vacuolation, & dilatation of PCTs, and DCTs (thick arrow & thin notched arrows respectively), shrinkage & rupture of the glomerulus (G) with widened urinary space, hypercellularity and cellular debris. (C&D) MSG + atorvastatin / Nigella Sativa treated rats showed near normal structure, intact glomeruli (G) and glomerular membranes, PCTs, and DCTs (thick & thin notched arrows respectively). However, some damage in the PCT and DCTs were still observed mostly in atorvastatin group. A: control group; B: MSG group; C: MSG+ atorvastatin group; and D: MSG + Nigella sativa group. (Hx.&E. X400) Scale bars, 100 µm.

**Masson trichrome stained sections:**

The rat kidney showed marked deposition of collagen fibres in MSG exposed rat kidney in comparison to control group while concomitant administration of Nigella sativa/atorvastatin reduces collagen deposition in comparison to MSG exposed rats (Figure 2).

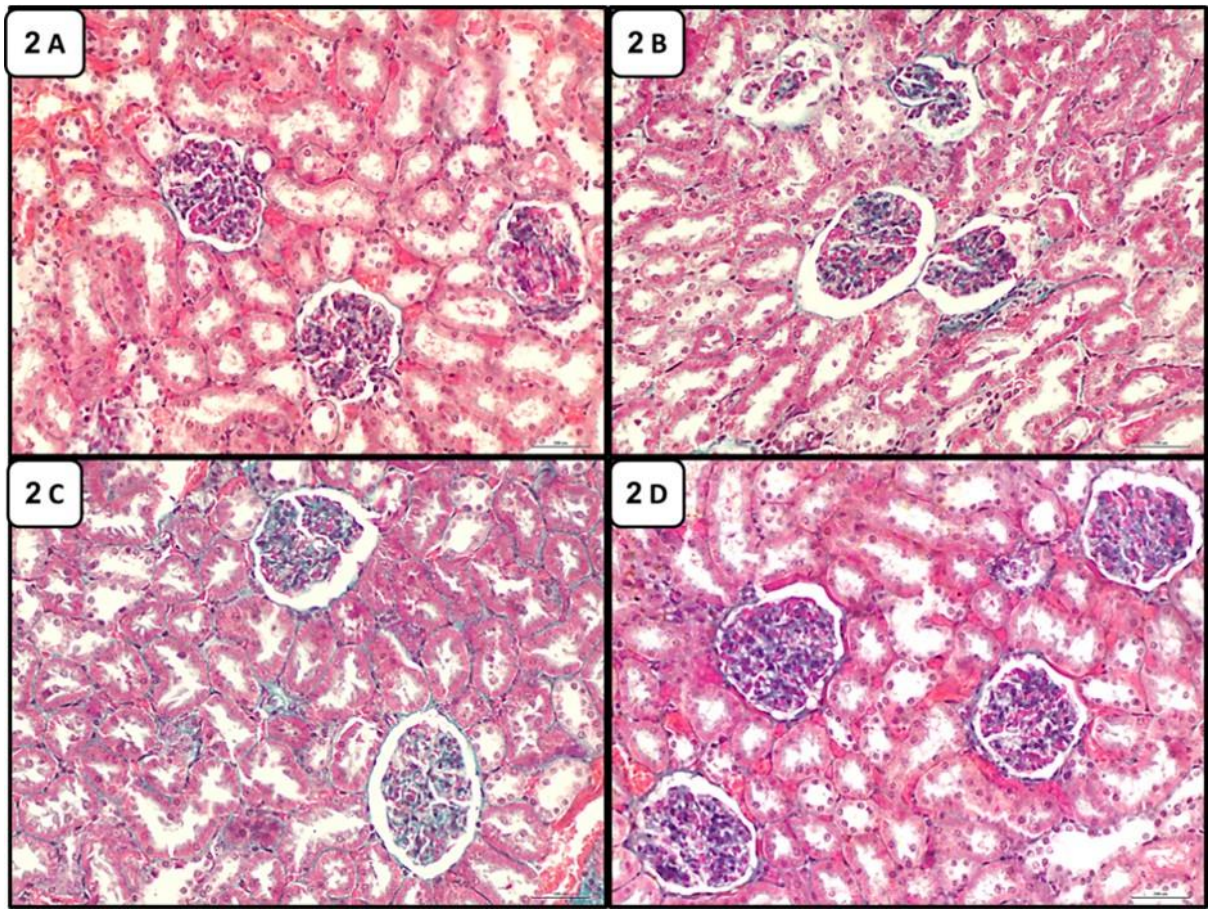


**Figure (2):** Nigella sativa/atorvastatin reduces collagen deposition and tubulointerstitial fibrosis in a rat model of MSG induced renal injury. A: Control group; B: MSG group; C: MSG+ atorvastatin group; and D: MSG + Nigella sativa group. (M.trichrome stain. X400) Scale bars, 200 µm.

**Immunohistochemical assessment of caspase 3:**

The rat kidney showed marked deposition of caspase 3 in MSG exposed rat kidney in comparison to control group while concomitant administration of Nigella sativa/atorvastatin reduces caspase 3 deposition in comparison to MSG exposed rats (Figure 3).

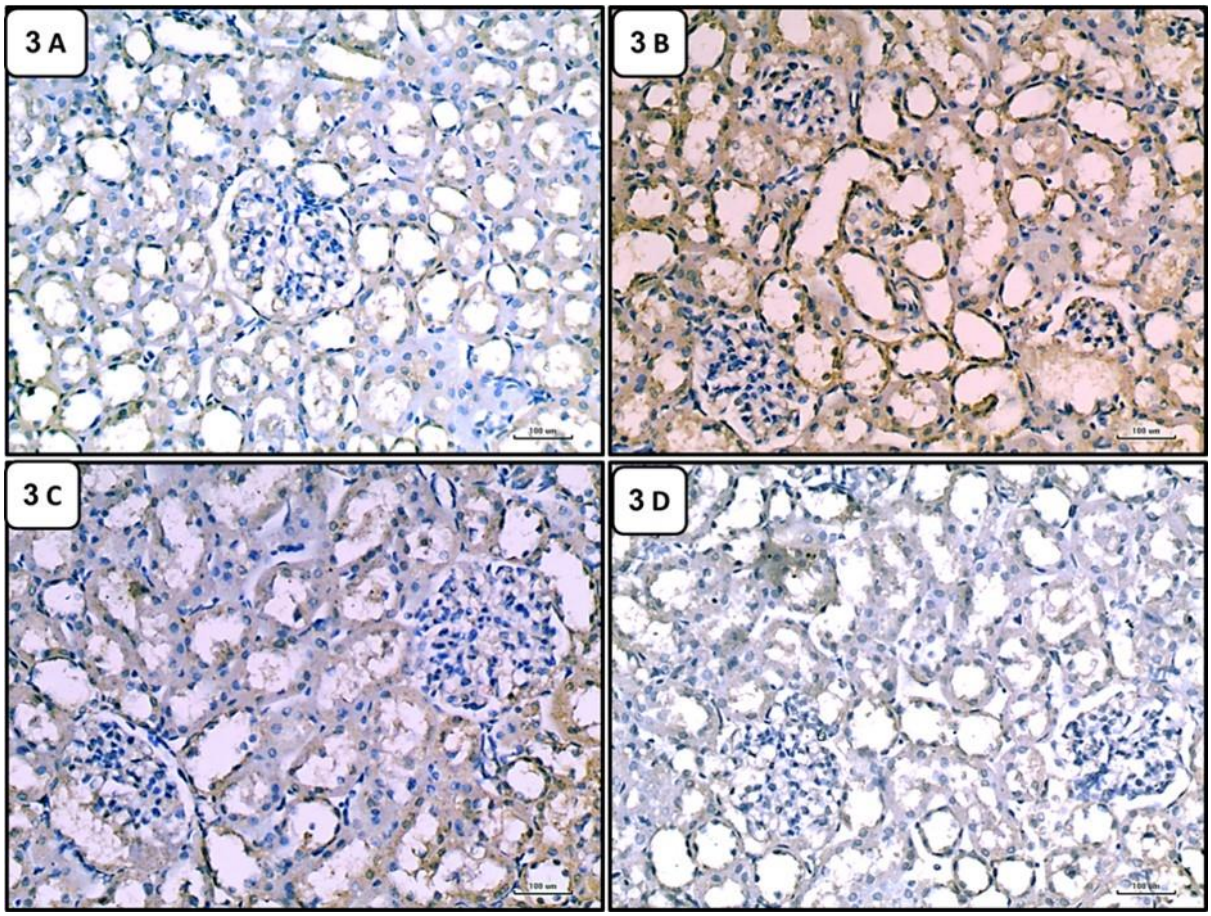


Figure (3): **Photomicrographs of Immunostained kidney sections for caspase-3** (A) **control group** showing weakest expression of caspase-3. marked expression of caspase-3 in MSG group (B); weak expression of caspase-3 in treated groups with Nigella sativa/atorvastatin group (C, D). A: Control group; B: MSG group; C: MSG + atorvastatin group; and D: MSG + Nigella sativa group. (Caspase 3 immune stain. X400) Scale bars, 100 µm.

**DISCUSSION**

Monosodium glutamate (MSG) is a water-soluble salt of glutamate, commonly used as taste enhancer, added to several foods as canned vegetables, soups and processed meat**(Egbuonu et al., 2021).**However, recent data showed that the average daily MSG intake is 3–4 g and that every additional gram of MSG increases the risk of developing metabolic syndrome due to their massive consumption and daily human exposure in our foods without determining the safe limit**(Celestino et al., 2021).**The kidney is the most affected organ by MSD consumption because, it is the main organ responsible for the detoxification of foreign substances in the body and have an essential role in disposal of waste products and regulating body homeostasis **(Elbassuoni et al., 2018).**Moreover that, the kidney possesses many glutamate receptors which modify its function by changes in the function of renal vasculature **(Kakoki et al., 2006).**

The results of this study found that MSG administration for two weeks induced hazardous structural changes to the kidney which affected its functions as revealed in the serum biochemical results of kidney function on exposure to MSG, there was marked increase in serumurea, uric acid and creatinine, in MSG-treated group compared to other control group. These results suggest that kidney dysfunction due to consumption of MSG and are in agreement with other studies **(Ortiz et al., 2006, El-Shenawy et al., 2019).**

In contrary to our results, previous studies showed no increase in the serum creatinine level in rats exposed to MSG alone**(Anuforo et al., 2020, Voits et al., 1996).**The difference in those studies could be due to variation in other factors which affect the serum level of creatinine as difference in age, sex, diet, weight, environment and time of the study.

Alongside the biochemical results of kidney function of MSG-treated group in this study, the structural changes are prominent in the same group as it showed distortion of one glomerulus, the other glomerulus showed widening of urinary space, increased vacuolization, damaged and vacuolated PCTs and DCTs with wider lumen. Similar to our histological results, Vercoutere et al. **(Vercoutère et al., 2004)**observed degenerative changes in the lumen of the renal tubules (PCT&DCT)and in Bowman's corpuscles, this could cause the defect in the tubular reabsorption, renal blood flow, and glomerular filtration rate, which could be due to nephrotoxic effect of MSG which resulted inkidney dysfunction and cellular damage.

In this study, the kidney structure revealed a correlation between the progressive damage and the lipid peroxidation products in the form of increased (MDA) levelas a response of the kidney damage, this was recently found by **(El-Hashash, 2021),**similar to our results. The previous data indicatedthe main cause of kidney damage on exposure to MSG consumption is the oxidative stress through increased activity of α-ketoglutarate dehydrogenase (a potential ROS generator) by the glutamate salt. Also, the increased level of intracellular calcium by glutamate receptors may enhance the generation of free radicals and inhibit the cystine uptake causing decreased GSH levels which lead to increased production of ROS causing nephrotoxicity **(Sharma, 2015).**

In the present study, the increase in MDA level is also associated with decrease in the activity of SOD antioxidant enzyme, which represent a marker of cell damage according to **(Zahra et al., 2013),** who stated that the increased level of ROS in the body and decreased antioxidants activityare primary initiators of cellular damage whereas, inhibition of membrane transport protein and increased lipid peroxidation are indicators of cell damage. These results prove the oxidative property of MSG on the kidney.

In this study, excess collagen fibers were observed in Masson's trichrome-stained kidney sections of MSG group which indicate the presence of fibrosis and there was significant increase in percentage of fibrotic area in comparison to control group. Similar study showed renal interstitial fibrosis in rats exposed to MSG**(Sharma et al., 2013).** The oxidative stress caused by MSG exposure may result in the observed renal fibrosis as ROS can enhance the transformation of fibroblasts into myofibroblasts, which produce more collagen fibers **(Sampson et al., 2011).** Immunostaining for caspase 3 reaction in the kidney, was done in this study to detect apoptosis, showed marked renal tissue expression of caspase-3 of MSG exposed rats than the control group which indicate that MSG induce apoptosis in the rat kidney. These findings were in agreement with the findings of Abd-Ella and his colleagues**(Abd-Ella et al., 2016)** who found an elevation in caspase-3 reaction in the liver and testis of MSG-treated rats. Caspase-3 is an apoptotic mediator which occurs through extrinsic and intrinsic pathways. Both pathways cause activation of caspase-3 that induce dramatic structural and biochemical changes of apoptosis**(Sarhan and ultrastructure, 2018).**From the above findings, the increase in caspase-3 expression on exposure to MSG indicate apoptotic changes which might be induced by production of oxidative stress products.

In our study, MSG+ nigella sativa/atorvastatin groups revealed improvement of the structural, and biochemical functions of the renal tissue withsignificant reduction of MDA level, area percentage of fibrosis, expression of caspase-3 and increased production of SOD were observed in comparison to MSG group. Similar to our study NS/atorvastatin succeeded in ameliorated the

structural and functional disturbances in the rat kidney exposed to amikacin induced Nephrotoxicity **(Abdel Fattah et al., 2020).**Such improvement suggests the protective mechanisms of nigella sativa/atorvastatin which could be explained by their antioxidant actions and decreased oxidative stress products in kidney tissue. The antioxidant effect of NS may be caused by improving glutathione redox cycle and inhibiting lipid peroxidation, stimulation and up-regulation ofgene expression of enzymatic antioxidants and scavenging free radicals by thymoquinone, which could stimulate a reduction in lipid peroxidation with amelioration ofthe harmful effects of MSG **(Abd-Elkareem et al., 2021).**Also, Statins as atorvastatin and its metabolites decrease oxidation of lipoproteinsin many oxidative systems and ameliorate free radical injury, which indicates an antioxidant activity against hydroxide and peroxyl radicals **(Ozbek et al., 2009).**

The protective effects produced by nigella sativa oil in association with MSG in our study are more prominent in comparison to MSG+ atorvastatin combination which indicate the more anti-oxidant and anti-apoptotic properties of nigella sativa comparable to atorvastatin. This was in agreements with previous study recorded on kidney tissue**(Abdel Fattah et al., 2020).**

**In conclusion:** MSG induced kidney toxicity through both oxidative stress production and apoptotic changes in the kidney but, Nigella sativa/atorvastatin are thought to be natural/syntheticne phro protective elements that efficiently relieve then ephrotoxicity via antiapoptotic and antioxidant activities.

**Conflict of interest:** none

**Financial disclosure:** nothing to be disclosed.

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