Date (*Phoenix dactylifera* L.) seeds extract mitigates the hepato-renal toxicities induced by monosodium glutamate in male albino mice

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مجلة البحوث في مجالات التربية النوعية

معرف البحث الرقمي DOI: 10.21608/jedu.2022.170217.1766

المجلد الثامن العدد 42 . سبتمبر 2022

الترقيم الدولي

P-ISSN: 1687-3424 E- ISSN: 2735-3346

موقع المجلة عبر بنك المعرفة المصري https://jedu.journals.ekb.eg/

موقع المجلة http://jrfse.minia.edu.eg/Hom

العنوان: كلية التربية النوعية . جامعة المنيا . جمهورية مصر العربية

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Abstract

Food additives like monosodium glutamate (MSG) are widely used; however, it causes several health problems. MSG may be administered safely if the negative effects are reduced by natural products. This study aimed to evaluate the phytochemical composition and the protective effect of *Phoenix dactylifera* seed extract (PDSE) against MSG hepato-renal toxicities in mice. The phytochemical compositions of PDSE were determined by quantitative method and GC/MS analysis. To determine the protective effect of PDSE, thirty-six male CD-1 mice were divided into three groups (n=12): The first group (Gp1) served as a negative control. Gp2 had administered with MSG (60 mg/kg) orally for 2 months. Gp3 had administered with MSG as in Gp2 then administered with PDSE (100 mg/kg) daily for two months. The results showed that the total phenolic and flavonoid contents of PDSE were 4.25 ± 0.35 g GAE/100g DW and 2.67 ± 0.16 g QUE/100g DW, respectively. The total antioxidant capacity was 125 ± 1.52 mg/ml. In addition, DPPH % was 78 %. GC-MS analysis showed the presence of 11 phytochemical components of PDSE. Administration of MSG led to an increase in the percentage of body weight (53.56% Vs 74.67%). PDSE treatment led to a decrease in the % of b. wt (61.45%). MSG administration led to alterations in hematological, biochemical, and histological parameters. However, treatment with PDSE post MSG led to significant improvement of these parameters. Collectively, the study showed the potential therapeutic effect of PDSE against the hepato-renal toxicities induced by MSG.

Keywords: Natural products, Food additive, Toxicity, Ameliorative, Experimental Animals.

Introduction

In the food industry, food additives are used to enhance the taste, flavor, color, appearance, and texture of food **(Moldes *et al.*, 2017)**. As a taste enhancer and stabilizer, in processed foods, one of the most often used additives (E621) is monosodium glutamate (MSG). **(Hajihasani *et al.*, 2020)**. Along with being utilized in sauces, salad dressings, and meats, MSG is also used to prepare and store food. MSG can therefore be ingested in enormous amounts at one meal without the consumer being aware of it **(Geraldine, 1982)**. Several studies have shown that long-term MSG use has negative effects on different organs, including the liver, kidney, pancreas, brain, and male gonads (**Ortiz *et al.*, 2006; Ugur Calis *et al.*, 2016; Onakewhor *et al.*, 2017)**. MSG also can cause several disorders such as obesity and diabetes **(Hajihasani *et al.*, 2020)**. MSG has been shown to have toxic effects on the kidney and liver **(Nwaopara *et al.*, 2008)**. Damage from MSG to several organs' mechanisms of action is related to the induction of oxidative stress **(Umukoro *et al.*, 2015)**. Increased levels of glutamine after MSG treatment may be the cause of lipid peroxidation (LPO) increment levels. By altering the cellular redox potential and encouraging lipogenesis, glutamine may start the oxidation of lipids **(Malik and Ahluwalia, 1994)**.

Vital organs such as the testis, liver, kidney, lung, and spleen have glutamate receptors. The ingested glutamic acid might go to glutamate receptors and causes a negative or poisonous reaction in these tissues **(Soliman, 2010)**. Therefore, some countries, including the United States, Mexico, and Canada have banned the use of MSG in the food industry due to rising concerns about the consumption of MSG and the risk of obesity. However, some other countries increased their consumption of MSG, especially in foods like soup, rice, noodles, and potatoes **(Kazmi *et al.*, 2017)**. MSG may be administered safely if the negative effects are reduced by natural products **(Suneetha *et al.*, 2013)**. Natural antioxidants have been shown to reduce the toxicity caused by MSG in several investigations **(Beyreuther *et al.*, 2007)**. **Shivasharan *et al.* (2013)** exhibited the flower extract of *Calendula*

officinalis had protective effects against oxidative stress caused by MSG and brain damage in mice. *Hibiscus sabdariffa* extract had anti-mutagenic properties against MSG-induced DNA damage in male Wistar mice, according to **Gheller *et al.* (2017)**. Date (*Phoenix dactylifera* L.) is one of the most cultivated trees around the world. Date is commonly cultivated in both semi-arid and dry areas **(Bouhlali *et al.*, 2018)**. From this, it can be calculated that around 863000 tonnes of seeds are thrown away each year as waste. Utilizing such a by-product could be crucial for date agriculture **(Al-Farsi and Lee, 2008)**. Date seeds are used as an ingredient in traditional medicines to treat liver problems, ague, and toothaches. It has a great interest in biomedical applications due to its high content of bioactive compounds **(Bouhlali *et al.*, 2015)**. Through the modulation of anti-inflammatory, antioxidant, and anticancer activities, date seeds have shown therapeutic efficacy in the prevention of several types of disease **(Rahmani *et al.*, 2014)**. According to a study by **Mohammad *et al.* (2014)**, date seed extract treatment dramatically boosted the paraoxonase and arylesterase activity in hypercholesterolemic mice. Therefore, the current study was carried out to determine the phytochemical compositions, antioxidant capacity, and the potential therapeutic effects of *P. dactylifera* seeds extract (PDSE) against the hepato-renal toxicity that induced by MSG in male mice.

Materials and methods

Chemicals

Monosodium glutamate (MSG) was purchased from Merck company (Germany). Gallic acid, quercetin, aluminum chloride, saponin, 2,2-diphenyl-1-picrylhydrazyl (DPPH), phosphomolybdenum were purchased from Sigma (St. Louis, Mo., USA). Aspartate and alanine aminotransferases (AST and ALT), urea, creatinine, superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), kits were purchased from Bio-diagnostic Company, Cairo, Egypt.

Preparation of date seeds extract

Date seeds were taken from the date fruits bought from Tanta city, Egypt, then moved to the Faculty of Science, Tanta University. Seeds were washed twice before being dried in the shade. The dried seeds were ground in a mechanical mortar, and 50 g of the powder was added to 500 ml of 70% ethanol before being left for three days. The supernatants were filtered and left to dry to get the hydro-alcohol *P. dactylifera* seeds extract (PDSE) for further use **(El-Naggar *et al.*, 2021)**.

Determination of the phytochemical constitutes in PDSE

Total phenolic (TP), flavonoids, saponin, DPPH free radical scavenging activities, and total antioxidant capacity (TAC) were determined either by quantitative analysis in PDSE. According to **Miliauskas *et al.* (2004)**, the TP contents from the extract were estimated. According to **Zhishen *et al.* (1999)**, the total flavonoid concentration was determined using the chromatogram technique with aluminum chloride. Saponin content was estimated according to **Hiai *et al.* (1976)** method. For the determination of DPPH free radical scavenging activity, the method reported by **Asnaashari *et al.* (2011)** was used. Total antioxidant activity was estimated by phosphomolybdenum assay according to **Prior *et al.* (2005)**.

Gas chromatography-mass spectrometry analysis

The chemical compositions of PDSE were determined using Thermo Scientific's Trace GC 1310-ISQ mass spectrometer (Alexandria, Egypt) with TG-5MS direct capillary column (30 m 0.25 mm 0.25 m film thickness). The temperature of the column oven was initially maintained at 50 °C, and then it was raised by 7 °C/min to 230 °C, held for 2 minutes, and then increased to the final temperature of 300 °C by 30 °C/min, held for 2 minutes. Temperatures of 270 °C and 260 °C, respectively, were maintained for the injector and MS transfer lines. As a carrier gas, helium was used at a 1 m/min constant flow rate. The Auto Sampler AS1300 with GC in the split mode automatically injected diluted samples of 1 µl with a 3-minute solvent delay. At 70 eV ionization voltages, full scan mode EL mass spectra were

collected over the range of m/z 45 -600. The temperature of the ion source was fixed at 200 °C. By comparing the components' retention times and mass spectra to those of the mass spectral databases WILEY 09 and NIST 11, the components were identified **(Qadir *et al.*, 2017)**.

Experimental design

Thirty-six male albino mice (20 ± 2 g) were purchased from National Research Center (NRC, Cairo, Egypt). Five animals were housed in each cage, and they were kept in a 12 h/24 h dark/light cycle with controlled humidity and temperature. The animal care and use committee of Tanta University's Faculty of Science gave its approval for the experiments' conformity with ethical standards (IACUC-SCI-TU-0252). Mice were housed for a week before to the experiment to allow for acclimatization. Sixty male CD-1 mice were divided into three groups (n=12): The first group (Gp1) served as a negative control, and Gp2 was orally administered with MSG at 60 mg/kg. Gp3 had administered with MSG as in Gp2, then treated orally with PDSE (100 mg/kg) daily for two months. All mice were sacrificed, and the blood was collected for the hematological and biochemical analyses, The tissues of the liver and kidney were harvested and fixed for histopathological investigations.

Determination of body weight changes percentage

To determine the percentage of the body weight (% b.wt) change, weights were taken at the beginning (initial b.wt) and at the end of the experiment (final b.wt) for each group. The % b.wt was calculated as follows: (final b.wt – initial b.wt / initial b.wt) × 100 (**El-Naggar *et al.*, 2021)**.

Determination of the hematological and the biochemical parameters

From the fresh blood samples of all groups, the electronic blood counter was used to calculate the total red blood cells (R.B.Cs), hemoglobin concentration (Hb g/dl), total platelets, white blood cells (W.B.Cs), and differential leucocyte counts. The activities of

AST, and ALT, levels of urea, and creatinine were measured in the serum samples. Additionally, the hepatic SOD, CAT activities, and MDA level were assessed using bio-diagnostic kits according to **Nishikimi *et al*. (1972), Aebi (1984), and Esterbauer and Cheeseman, (1990)**, respectively.

Histopathological investigations

The liver and kidney tissue slices were immediately collected, finely cut, and preserved in 10% formalin for 24 hours following animal sacrifice under appropriate anesthesia using Iso-fluran (100%). After being cleansed, the tissue samples were dehydrated in increasing serial ethanol concentrations, and the surplus fixative was removed by cleaning with xylene thereafter. Paraffin wax was used to encase tissue slices. Haematoxylin and eosin (H&E) staining was applied to mounted sections of 5 m thickness for histopathological observations. Each organ's slides were created and examined for histopathological changes microscopically **(Bancroft and Layton, 2013)**.

Statistical analysis

To assess the significant differences between treatment groups, an ANOVA with a one-way analysis of variance was used. To show the significant impact of therapy, the Tukey test was used to compare each group to the control group. The threshold for statistical significance was established as $p \leq 0.05$. All information is presented as mean SD.

RESULTS

Phytochemical compositions of PDSE

As shown in table 1, the results showed that the total phenolic and flavonoid contents of PDSE were 4.25 ± 0.35 g GAE/100g DW and 2.67 ± 0.16 g QUE/100g DW, respectively. Furthermore, the saponin level was 143.58 ± 3.76 mg/100g DW. While the TAC was 125 ± 1.52 mg/ml. In addition, DPPH % was 78 % and their $IC_{50}$was 3.78 ± 0.37 mg/ml.

Table 1. Quantitative phytochemical analysis of *Phoenix dactylifera* seeds

Phytochemical analysis	*Phoenix dactylifera L.* seeds
Total phenolic (g GAE/100g DW)	4.25 ± 0.35
Total flavonoids (g QUE/100g DW)	2.67 ± 0.16
Saponin (mg/100g DW)	143.58 ± 3.76
TAC (mg/ml)	125 ± 1.52
DPPH scavenging %	78 % ± 1.67
IC_{50} of DPPH (mg/ml)	3.78 ± 0.37

DW: Dry weight, GAE: Gallic acid equivalent, QUE: Quercetin equivalent. TAC: Total antioxidant capacity, IC_{50}: Inhibitory concentration 50%.

GC-MS analysis of PDSE

As shown in table 2, GC-MS analysis showed the presence of 11 phytochemical components of PDSE. The peak area (%) of dodeca-1,6-dien-12-ol, 6,10 dimethyl, 13-Tetradece-11-yn-1-ol, 12-Methyl-E,E-2,13-octadecadien-1-ol, 1-(cyclopropyl-nitro-methyl)-cyclopentanol, 8,11,14-Eicosatrienoic acid, (Z,Z,Z), Ethyl iso-allocholate, Octadecanoic acid, 9,10-epoxy-18 (trimethylsiloxy), methyl ester, 1-Heptatriacotanol, and 9,12,15-Octadecatrienoic acid, 2,3-dihydroxypropyl ester, (Z,Z,Z) were 13.10, 3.91, 3.39, 2.07, 2.48, 5.80, 2.53, 21.07, and 53.49%, respectively.

Table 2. GC-MS analysis of *Phoenix dactylifera* seeds extract.

No.	RT (min.)	Name	M. F.	M. Wt	Peak area %
1	24.61	11-Dodecen-2-one	$C_{12}H_{22}O$	182	1.03
2	25.51	2-methyl-10-undecenal	$C_{12}H_{22}O$	182	1.14
3	26.83	Dodeca-1,6-dien-12-ol, 6,10 dimethyl	$C_{14}H_{26}O$	210	3.10
4	27.46	13-Tetradece-11-yn-1-ol	$C_{14}H_{24}O$	208	3.91
5	31.04	12-Methyl-E,E-2,13-octadecadien-1-ol	$C_{19}H_{36}O$	280	3.39
6	31.41	1-(cyclopropyl-nitro-methyl)-cyclopentanol	$C_9H_{15}NO_3$	185	2.07
7	31.97	8,11,14-Eicosatrienoic acid, (Z,Z,Z)	$C_{20}H_{34}O_2$	306	2.48
8	32.61	Ethyl iso-allocholate	$C_{26}H_{44}O_5$	436	5.80
9	33.27	Octadecanoic acid, 9,10-epoxy-18 (trimethylsiloxy), methyl ester	$C_{22}H_{44}O_4Si$	400	2.53
10	33.87	1-Heptatriacotanol	$C_{37}H_{76}O$	536	21.07
11	34.22	9,12,15-Octadecatrienoic acid, 2,3-dihydroxypropyl ester, (Z,Z,Z)	$C_{21}H_{36}O_4$	352	53.49

RT: Retention time, M.F.: Molecular formula, M.Wt: Molecular weight.

Effects of PDSE treatment on the % of the body weight change

The results treatment of mice with MSG led to significant increase ($p \leq 0.05$) in the % of b.wt change (74.67%), when compared to the negative control group (53.56%). The MSG-treated mice that were received PDSE showed a reduction ($p \leq 0.05$) in the % b.wt change (61.45%) when compared to the MSG-treated mice alone (Figure 1).

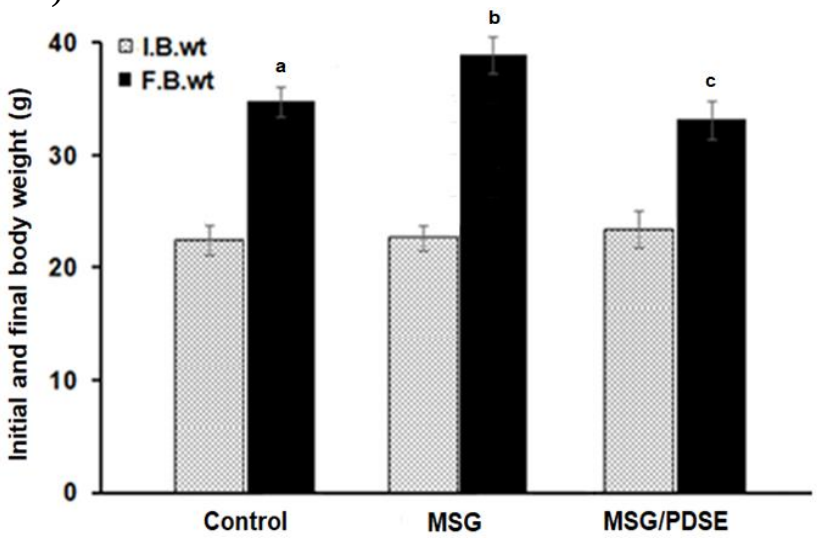

Figure 1. Initial (I.B.wt), final body weight (F.B.wt) and % b.wt changes in the different groups under the study.

Impact of the treatment with PDSE on the hematological changes of MSG-treated mice

As compared to the control group, hemoglobin (Hb) concentration and total red blood cell (R.B.C.) counts were decreased in the MSG-treated mice ($p \leq 0.05$). The total platelets count was considerably higher ($p \leq 0.05$) in the MSG-treated mice when compared to their control. Treatment of MSG-treated mice with PDSE, however, restored the values of R.B.Cs and Hb close to the normal values (Table 3A). When compared to the control group, the MSG-treated mice showed a significantly higher total white blood cell (W.B.C.) count ($p \leq 0.05$). Treatment of MSG-treated mice with PDSE, however, restored their count near the control group (Table 3B).

Table 3A. The total count of RBCs, Hb levels, and the total platelets count in different groups under the study.

Groups	RBCs (x10^6/µL)	Hb (g/dL)	Platelets (x10^3 /µL)
Control	9.576 ± 1.25 [a]	13.87 ± 1.89 [a]	745 ± 78 [a]
MSG	6.21 ± 1.19 [b]	10.21 ± 1.23 [b]	967 ± 86 [b]
MSG/PDSE	8.58 ± 0.98 [a]	12.89 ± 1.16 [a]	857 ± 75 [c]

The values represented means ± S.D.; means that do not share a letter were significantly different (p<0.05). MSG: Monosodium glutamate, PDSE: *Phoenix dactylifera* seeds extract, RBCs: Red blood cells, Hb: Hemoglobin.

Table 3B. Total WBCs count and differential count in different groups under the study.

Groups	WBCs (×10^3/ul)	% of the differential count		
		Neut.	Lymph.	Mono.
Control	7.45 ± 1.13 [a]	24.51 ± 2.15 [a]	83.76 ± 4.36 [a]	2.87 ± 0.63 [a]
MSG	13.76 ± 0.95 [b]	18.75 ± 0.96 [b]	89.97 ± 6.14 [b]	2.53 ± 1.24 [b]
MSG/PDSE	8.95 ± 1.02 [a]	12.93 ± 1.21 [a]	82.65 ± 3.95 [a]	3.27 ± 0.79 [a]

The values represented means ± S.D.; means that do not share a letter were significantly different (p<0.05). MSG: Monosodium glutamate, PDSE: *Phoenix dactylifera* seeds extract, WBCs: White blood cells.

Effect of PDSE treatment on the liver and kidney functions of MSG-treated mice

MSG treatment led to a significant increase in the serum activities of AST and ALT as compared to the control group. Treatment with PDSE after MSG, however, decreased liver function transaminases (AST and ALT) activities compared to mice that were treated with MSG alone. Serum creatinine and urea levels were increased ($p \leq 0.05$) in the MSG-treated mice, however, PDSE treatment post-MSG administration resulted in an improvement in their levels (Figure 2).

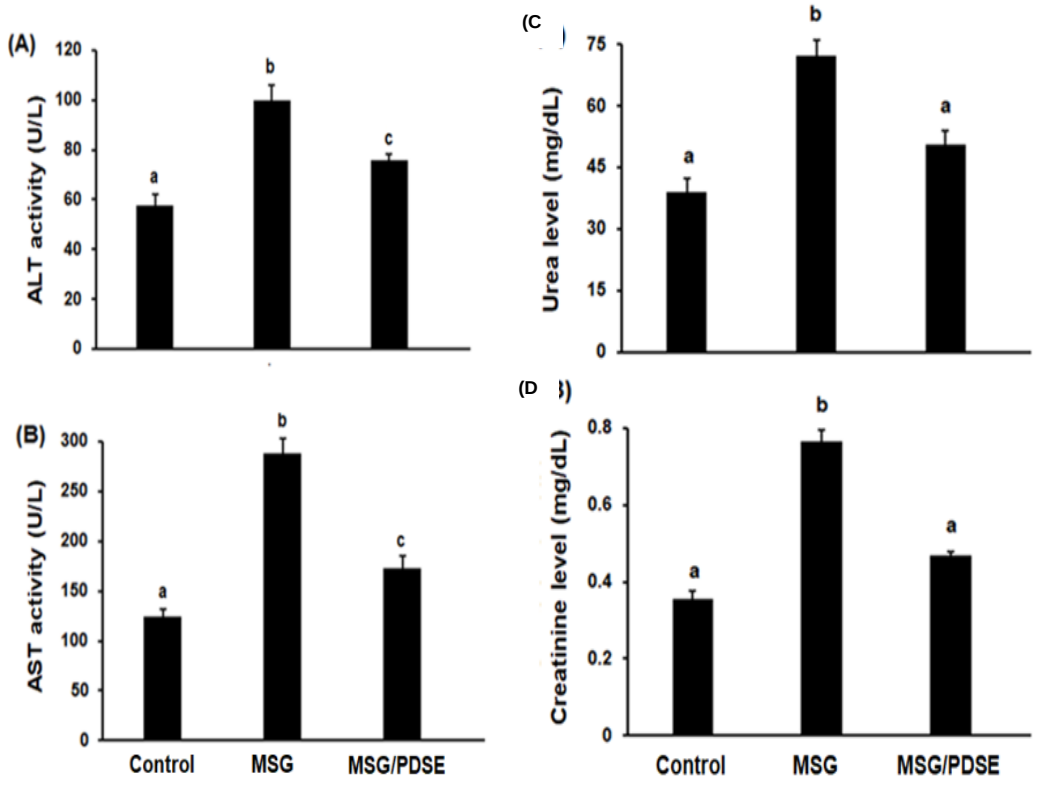

Figure 2. Serum transaminases (ALT, AST) activities and kidney function biomarkers in the different groups under the study, ALT (A), AST (B), Urea (C), and creatinine (D) levels.

Impact of the treatment with PDSE on the antioxidants/oxidants status

As shown in figure 3, SOD and CAT activities were markedly decreased in the MSG-treated mice; however, MDA levels were increased when compared to their levels in normal control mice. Treatment of MSG-administered mice with PDSE led to a significant increase in the SOD and CAT activities a significant decrease in the level of MDA ($p \leq 0.05$).

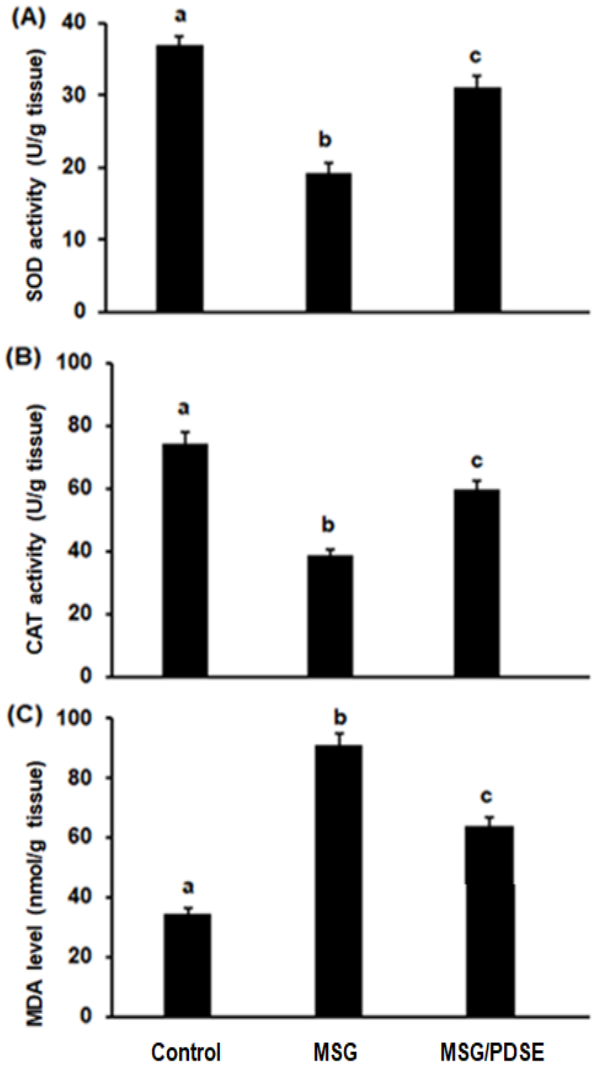

Figure 3. Hepatic antioxidants/oxidants biomarkers (SOD, CAT, and MDA) in the different groups under the study, SOD activity (A), CAT activity (B), and MDA levels (C)

Effect of the treatment with PDSE on hepatic and renal architectures from MSG-toxicity

Hepatic lobulation and normal liver architecture were seen in the liver of the control group. Kupffer cells-containing endothelium layer cells cover the narrow blood sinusoids that alternate with the hepatic strands. Hepatocytes have a polyhedral shape and contain homogeneously pigmented granular cytoplasm. The spherical nuclei of the hepatic cells are centrally placed, have a defined

nuclear envelope, and have one or more conspicuous nuclei, occasionally along with a significant number of chromatin granules (Figure 4a). Liver sections of PDSE treated group showed hepatic architecture with a normal-like configuration; normal cords of hepatocytes radiating from a normal central vein with normally organized nuclei, others with megakaryocytic ones and blood sinusoids with distinctive Kupffer cells that phagocytose (Figure 4b). Several histopathological observations were noticed in liver sections of MSG administered mice, represented by pronounced disarray of the hepatic architecture and irregular distribution of hepatic cords around the congested and dilated central veins, some nuclear changes were noticed like karyolitic ones and blood sinusoids were irregular with distinct and activated phagocytic Kupffer cells (Figure 4c). Treatment of MSG-administerd mice with PDSE showed an improvement of the hepatic structure evidenced by normal radiating hepatocytes with normal central nuclei with homogenous cytoplasm and normal central vein. Few histopathological alterations were noticed were represented by few numbers of hepatocytes degenerated with cytoplasmic vacuolation and blood sinusoids with activating Kupffer cells (Figure 4d).

In control kidney sections, the glomerulus is bordered by two layers of epithelium and the Bowman's capsule in the renal parenchyma, which has a normal histological structure. The glomeruli are oval and circular, and simple epithelia surrounded the proximal convoluted tubules. These epithelia possessed an acidophilic cytoplasm and a profusion of microvilli at the apex that produced a brush-like border. Simple cuboidal epithelium lined the distal convoluted tubules (Figure 5a). The cortex that contains glomeruli in the PDSE-treated animals has a normal Bowman's space and most renal tubules appear normal; however, a small number of tubules have degenerated with the destruction and degeneration of their lining epithelia (Figure 5b). Kidney sections of mice administered with MSG showed disorganized kidney anatomy; disorganized glomeruli with irregular Bowman's space, normal renal tubule counts are low, others are poorly distinguished and destruction of its lining epithelia with intermixed contents and severe intratubular hemorrhage was

noticed (Figure 5c). Kidney sections of mice administered with MSG and treated with PDSE showed improvement of the renal profile represented by normal and organized glomeruli and mostly normal renal tubules were normal with normal lining epithelia, few ones are destructed and few intratubular hemorrhage and leukocytic infiltration were observed (Figure 5d).

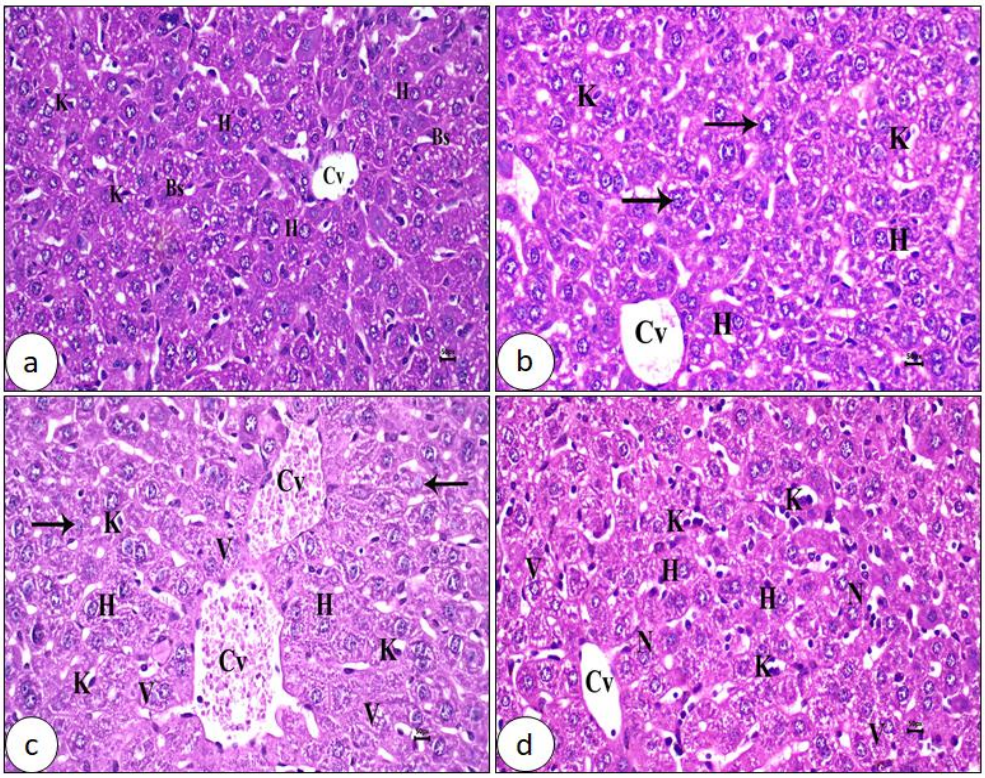

Figure 4. Photomicrographs of liver sections of different experimental groups stained with H&E. a). Liver section of control mice showing normal hepatic architecture; normal central veins (Cv), hepatocytes are organized in hepatic cords (H) with normal centric nuclei with homogenous cytoplasm, normal blood sinusoids with normal Kupffer cells (K). b) Liver section of PSDE-treated mice exhibits a slightly widening central vein (Cv), normal radiating hepatocytes (H) with normal central nuclei, some hepatocytes with megakaryocytic ones (arrows), irregular blood sinusoids with distinct phagocytic Kupffer cells (K). c) Liver section of mice administered with MSG showing marked disorganization of hepatic architecture; dilated congested central veins (Cvs), few numbers of hepatocytes are normal (H), other hepatocytes with cytoplasmic vacuolation (V) and karyolitic nuclei (arrows), blood sinusoids with activated Kupffer cells (K). d) Liver section of mice administered with MSG and treated with PDSE showing

improvement of the hepatic architecture; normal central vein (Cv), normal radiating hepatocyte (H), few number of hepatocytes with vacuolated cytoplasm (V) and blood sinusoids with activated Kupffer cells (K) (X 400).

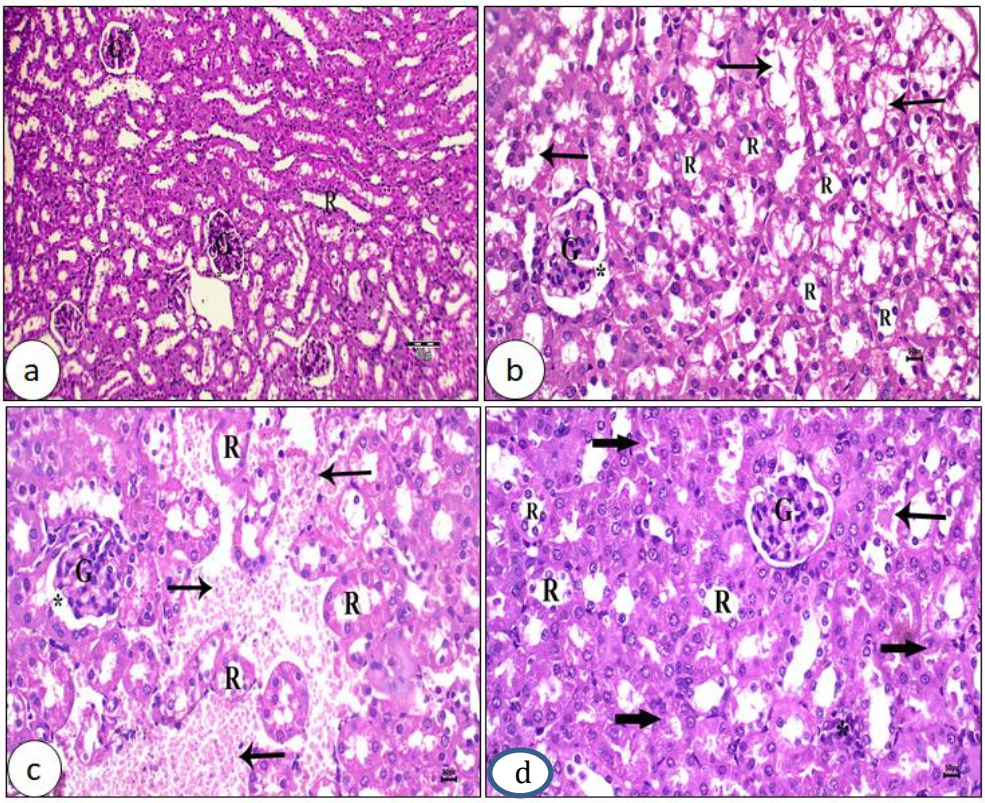

Figure 5. Photomicrographs of kidney sections of different experimental groups stained with H&E. a) Renal cortex of mice in the control group has a normal body structure of renal glomeruli (G) with regular Bowman's space (*) and normal renal tubules (R). b) Kidney section of PDSE-treated mice exhibits the normal structure of the renal architecture; normally organized glomeruli (G) with regular Bowman's space (*), mostly renal tubules are normal (R), few numbers are damaged (arrows) with atrophy and destruction of their lining epithelia. c) Kidney section of mice administered with MSG showing disorganized kidney anatomy; disorganized glomeruli with irregular Bowman's space (*), few numbers of renal tubules are normal (R), others are poorly distinguished with intermixed contents, severe intratubular hemorrhage was noticed (arrows). d) Kidney section of mice administered with MSG and treated with PDSE exhibits mild improvement; organized glomeruli (G), mostly renal tubules are normal (R), few numbers are damaged (thick arrow), few intratubular hemorrhages (arrow) and mononuclear infiltration were observed (*) (X 400).

DISCUSSION

Monosodium glutamate (MSG) is a food additive used in the food industry for processed meat, canned goods, chips, crispy chicken, noodles, seasonings, and fast food at chain restaurants **(Hajihasani *et al.*, 2020)**. Using MSG as a food additive in higher doses, for longer periods causes considerable toxic effects on vital organs, which ultimately results in cellular damage **(Othman and Bin-Jumah, 2019)**. For instance, the high dose of MSG has been linked to a number of health problems, including brain cells destruction, an increase in heart rate, and the development of Alzheimer's disease **(Prastiw *et al.*, 2015; Lopez-Miranda *et al.*, 2015; Miranda *et al.*, 2017)**. To overcome the toxicity of several food additives, natural ingredients are thought to be promising agents.

The by-product of the date makes up about 10% to 15% of the fruit weight **(Hussein *et al.*, 1998)**. These by-products were proven as antidiabetic, antioxidant, and antiviral agents **(El-Fouhil *et al.*, 2010; Habib *et al.*, 2011)**. In addition, a previous study reported that the PDSE has tremendous promise for pharmaceutical applications, including the development of antibacterial and anticancer drugs **(Dhevi *et al.*, 2017)**. These therapeutic potentials could be due to their different effective phytochemical components including phenolic, flavonoids, and saponin. The date seed contains alkaloids, flavonoids, tannins, saponins, phenol, and sterols **(Abiola *et al.*, 2016)**. The current study reported that PDSE has a potent antioxidant activity due to the presence of high contents of polyphenolic compounds. These findings were in agreement with the study by **Abiola *et al.* (2016)**. The analysis of GC-MS showed the presence of various phytochemical components in PDSE. **Azmat *et al.* (2010) and Benmeddour *et al.* (2013)** showed that the PDSE contains some steroids, terpenoids, cinnamic acid and its derivatives.

The results showed that MSG caused a notably higher % of b.wt change. It has been reported that MSG has some harmful effects on human and animal tissues through the induction of oxidative stress in different body organs **(Husarova and Ostatnikova, 2013; Henry-Unaeze, 2017)**. The current study was in harmony with **Kumbhare *et al.* (2015)** and **Ahmed (2016)** who revealed a

significant increase in body weight in MSG-treated rats as compared to the non-treated group. The treatment with PDSE post-MSG administration showed a significant decrease in the % b.wt change. This could be due to the potent antioxidant effect of PDSE to decrease the oxidative stress induced by MSG administration. This finding was consistent with **Mohamed *et al.* (2021)** who examined the effects of tannic acid protection against MSG toxicity on body weight in adult male rats. Moreover, the study reported that treatment of mice with MSG led to a significant decrease in the total R.B.Cs count, Hb concentration, and an increase in the total W.B.Cs count. Similarly, **Ghadhban, (2017)** reported that adult rats exposed to MSG had significant increases in body weight, W.B.Cs count.

The degree of hepatic toxicity induced by MSG was detected by measuring the serum activities of hepatic enzymes (AST and ALT) **(Ahmed *et al.*, 2019)**. The present results showed that the serum ALT and AST activities significantly increased after MSG administration. However, the treatment with PDSE after MSG administration decreased ALT and AST activities. Furthermore, the serum levels of urea and creatinine were dramatically elevated in the MSG-treated mice, whereas they were significantly reduced in the PDSE-treated mice. More recently, **Bouhlali *et al.* (2021)** found that the administration of different dates seeds varieties extracts significantly reduced the levels of AST, ALT and ALP in a dose-dependent manner in paracetamol-induced liver toxicity rats. The restoration of liver function parameters by PDSE toward the normal values indicated that PDSE might have a protective effect against MSG toxicity might be attributed to their strong antioxidant capacity, preserving the hepatocellular membrane structural integrity and stabilizing plasma membranes which prevent liver injury **(Bouhlali *et al.*, 2021).**

Natural antioxidants have been shown to reduce the toxicity caused by MSG in several investigations **(Beyreuther *et al.*, 2007)**. MSG-treated mice showed a significant increase in the MDA levels while the SOD and CAT activities decreased significantly. **Henry-Unaeze, (2017)** reported that MSG causes oxidative stress, which has negative effects on both human and animal tissues. However, the treatment of the MSG-treated mice

with PDSE led to an improvement in antioxidant/oxidants status. These observations were in agreement with a previous study, which reported the enhancement of antioxidant enzyme activities upon administration of PDSE in experimental animals **(Al-Qurainy *et al*., 2017)**.

The administration of MSG led to histological changes in the liver and renal tissues. It has been reported that MSG was able to induce toxic effects on the kidney and liver **(Nwaopara *et al*., 2008)**. This could be due to the ability of MSG to increase reactive oxygen species (ROS) generation leading to oxidative damage in many tissues. Increased levels of glutamine after MSG treatment may be the cause of lipid peroxidation (LPO) increment levels. By altering the cellular redox potential and encouraging lipogenesis, glutamine may start the oxidation of lipids **(Malik and Ahluwalia, 1994)**. LPO due to MSG administration might cause morphological abnormalities in liver and kidney tissues. These findings were consistent with the previous study by **El-Hashash (2021)**. While MSG-administered and PDSE treatment led to improvement in the liver and kidney architectures. In traditional medicine, the powdered form of date seeds is used for dealing with liver diseases due to its high content of bioactive compounds **(Bouhlali *et al*., 2015)**. Furthermore, **El-Naggar et al. (2021)** reported that treatment with PDSE revealed marked improvement in hepatic and renal cellularity.

The result of this study demonstrated that date seed extract serves as a good source of natural antioxidants and were effective in preventing the deleterious effects of MSG administration, by improving liver and kidney functions as well as enhancing antioxidant status. The efficacy of PDSE might be attributed to its phenol, flavonoid contents and its strong antioxidant capacity which may support the traditional uses of date seeds and as functional foods. In conclusion, the current investigation showed the possible ameliorative impact of PDSE against the hepato-renal toxicities induced by MSG through the improvement of hematological, biochemical, and histopathological alterations.

Conflicts of Interest

There were no conflicts of interest to declare.

مستخلص نوى التمر (*Phoenix dactylifera* L.) يقلل من السمية الكبدية الكلوية المستحدثة بجلوتامات أحادي الصوديوم في ذكور الفئران البيضاء

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الملخص العربى

تعتبر جلوتامات أحادي الصوديوم (MSG) مادة مضافة غذائية شائعة الإستخدام، على الرغم من المشاكل الصحية المتعددة التي تسببها. هذا وتقلل المنتجات الطبيعية من هذه الآثار الضارة لها. وتهدف هذه الدراسة الى تحديد المركبات الفيتوكيميائية ومضادات الأكسدة والتأثير العلاجي لمستخلص نوى التمر على السمية المستحدثة بجلوتامات أحادي الصوديوم في الفئران. وقد تم تحديد المركبات الفيتوكيميائية بكل من الطرق القياسات الكمية ومقياس الطيف الغاز الكروماتوجرافي. و لتحديد الأثار العلاجية تم إستخدام ستة وثلاثين من ذكور الفئران وتم تقسيمها إلى ثلاث مجموعات (ن = 12)، حيث أن تم استخدام المجموعة الأولى كمجموعة ضابطة سالبة. وحقنت المجموعة الثانية جلوتامات أحادي الصوديوم (60 مجم / كجم) عن طريق الفم لمدة شهرين. وتم إعطاء المجموعة الثالثة جلوتامات أحادي الصوديوم كما في المجموعة الثانية ثم حقنت بمستخلص نوى البلح (100 مجم / كجم) يوميًا لمدة شهرين. أظهرت النتائج أن إجمالي محتويات الفينول والفلافونويد لـمستخلص نوى البلح (4.25 ± 0.35 جم و2.67 ± 0.16 جم لكل 100 جم من الوزن جاف)، على التوالي. وكانت السعة الكلية لمضادات الأكسدة (125 ± 1.52 مجم/مل). وأظهر تحليل مقياس الطيف الغاز الكروماتوجرافي وجود 11 مكونًا كيميائيًا نباتيًا من مستخلص نوى البلح. أدى إعطاء جلوتامات أحادي الصوديوم إلى زيادة نسبة وزن الجسم (53.56٪ مقابل 74.67٪). وأدى العلاج بمستخلص نوى البلح إلى انخفاض معنوي في نسبة وزن الجسم (61.45٪). وقد حدثت تغييرات في الدلائل الدموية والكيميائية الحيوية والنسيجية نتيجة لحقن جلوتامات أحادي الصوديوم. وقد أدى العلاج بمستخلص نوى البلح بعد إعطاء جرعات من الجلوتامات أحادي الصوديوم إلى تحسن كبير في هذه المعايير. والخلاصة أن العلاج بمستخلص نوى البلح قد ادى الى تحسن في كل من أنسجة الكبد والكلى في الفئران التي تجرعت بجلوتامات أحادي الصوديوم.

الكلمات المفتاحية: منتجات طبيعية، إضافات غذائية، سمية، تحسن، حيوانات تجارب.

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