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# Research Article
# Hepatorenal Protective Effects of Some Plant Extracts on Experimental Diabetes in Male Rats

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## Abstract

**Background and Objective:** Diabetes mellitus (DM) is a main worldwide health problem predisposing to noteworthy enhanced mortality. Currently, the therapeutic factors of DM associated with side effects, resistance, toxicity and high cost, so the use of medicinal plants for DM treatment is recommended. The present study investigated the possible therapeutic effects of the extracts of *Olea oleaster* and *Juniperus procera* leaves and *Opunita ficus-indica* stems on hepatorenal injury in streptozotocin (STZ) diabetic male rats. **Materials and Methods:** Diabetes mellitus was induced in experimental animals by a single intraperitoneal injection of STZ at a dose of 70 mg $kg^{-1}$. The experimental animals were divided into 8 groups. The experimental rats of group 1 were served as normal control. Rats of group 2 were served as diabetic control rats. Diabetic rats of groups 3, 4 and 5 were treated with the extracts of *O. oleaster*, *J. procera* and *O. ficus-indica*, respectively at a dose of 400 mg $kg^{-1}$ b.wt.,/day for 5 weeks. Non diabetic rats of groups 6, 7 and 8 were supplemented with *O. oleaster*, *J. procera* and *O. ficus-indica* respectively. At the end of the experiment, the blood, liver and kidney samples were collected from all groups for biochemical and histopathological examinations. **Results:** The levels of serum glucose, malondialdehyde, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine, blood urea nitrogen and uric acid were significantly enhanced, while the levels of serum glutathione, superoxide dismutase and catalase were significantly declined in diabetic control rats of group 2. Histopathological examination of liver and kidney in diabetic control rats showed severe changes. Supplementation of the studied plant extracts alleviated the hyperglycemic status, biochemical parameters of hepatorenal markers, oxidative stress indicators and histopathological changes of liver and kidney. **Conclusion:** These findings confirm that the hepatorenal protective effects of these extracts strongly related to the suppression of oxidative stress associated with DM. Moreover, the present study suggested that these extracts were safe and promising therapeutic factors for DM and its complications.

Key words: Diabetes mellitus, hepatorenal injury, *Olea oleaster*, *Juniperus procera*, *Opunita ficus-indica*, therapeutic factors, hepatorenal protective effects, diabetic rats

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Diabetes mellitus (DM) is a health problem affecting millions of individuals worldwide[1]. DM is the most prevalent form globally which is associated with elevated postprandial hyperglycemia. DM is considered an important factor in the development of many complications in diabetics such as hepatopathy and nephropathy. DM accelerates the occurrence of liver disorders by altering its physiology[2-5]. The physiological alterations of liver including carbohydrate, protein and lipid metabolism and changes in anti-oxidant status[6-8]. Diabetic nephropathy is a major complication of DM and a leading cause of end-stage renal failure throughout much of the world[9,10]. The severity of diabetic nephropathy is one of the major factors determining the prognosis of diabetic patients. Diabetic nephropathy is the major determinant of morbidity and mortality in patients with DM. Previous scientific reports showed that diabetic nephropathy induced by hyperglycemia via several mechanisms such as oxidative stress induction and increase of glycation reaction. The production of highly reactive oxygen radicals were attributed to oxidative stress which caused cells toxicity[11].

In spite of different types of anti hyperglycemic medicines are readily available to control the increase of blood glucose level. However, these medicines are known to have undesirable influences and side effects. Hence, the search for more effective and safer therapeutic agents of natural origin is continuing as it is considered valuable[12-14]. Hypoglycemic herbal medicines are still commercially manufactured as modern drugs, although they have had their therapeutic properties in the traditional drug regimens[15]. Olive trees, *Olea oleaster*, (family: Oleaceae), juniperus, Juniperus *procera*, (family: Cupressaceae) and cactus, *Opuntia ficus-indica*, (family: Cactaceae) were considered as medicinal plants due to the therapeutic effects of their constituents. Experimental studies have shown promising results of the effectiveness of these plants for the treatment and attenuation of various diseases[16-18]. In the current literature, there is no or no much comparative data concerning the effects of *O. oleaster* and *J. procera* leaves and *O. ficus-indica* stems extracts on physiological and histopathological alterations in diabetic animals and human. Therefore, the present study was undertaken to compare the influence of *O. oleaster* and *J. procera* leaves and *O. ficus-indica* stems extracts on STZ-induced DM and hepatorenal injury in male rats.

## MATERIALS AND METHODS

**Extraction processes:** Fine qualities of *O. oleaster* and *J. procera* leaves and stems of *O. ficus-indica* were directly collected from the outskirts of Albaha region of Saudi Arabia during March 2018. After washing and drying process, the plant samples were powdered and stored at -20°C until use for extraction. Eight liters of hot water were added to every 200 g of these plant samples and mixed for 4 h. Every mixture was slowly boiled for 90 min and cooled at room temperature. The mixed solutions were treated with an electric mixer for 30 min and filtered. The filtrates were evaporated in an oven at 40°C to produce dried residues (active principles). Calculations of the yields means were equal 21.3, 17.7 and 15.9% for *O. oleaster* leaves, *J. procera* leaves and *O. ficus-indica* stems extracts respectively compared with the powdered samples. Furthermore, the extraction processes were conducted every two weeks and the extracts were kept in a refrigerator for experimental treatments.

**Experimental design:** The experiments were conducted with Wistar male rats weighing 256-222 g. Male rats were housed in standard plastic cages with humidity (65%), temperature (20±1°C) and 12:12 h light: dark cycle of experimental room at the Experimental Animal Unit, Faculty of Sciences, King Abdulaziz University, Jeddah, Saudi Arabia. The rats had free access to standard commercial chow and water. The principles of laboratory animal care were followed through out the duration of experiment and instruction given by King Abdulaziz University Ethical Committee was followed regarding experimental treatments.

For DM induction, STZ (Sigma-Aldrich Corp, St. Louis, MO, USA) was intraperitoneally injected at a single dose of 70 mg $kg^{-1}$ body weight in overnight fasted rats. Fasting blood glucose levels were measured after 4 days in STZ injected rats. Diabetic rats were determined when the levels of glucose more than 17 mmol $L^{-1}$. Forty normal and 40 diabetic rats were divided in to 8 groups, each group consisting of 10 animals. Rats of group 1 were served as normal control and intraperitoneally injected with saline solution (0.9% NaCl). Rats of group 2 were served as diabetic control. Diabetic rats of group 3 were administered orally with *O. oleaster* leaves extract (OLE) at a dose of 400 mg $kg^{-1}$ b.wt./day. Diabetic rats of group 4 were supplemented with *J. procera* leaves extract (JLE) at a dose of 400 mg $kg^{-1}$ b.wt./day. Diabetic rats of group 5 were administered with *O. ficus-indica* stems extract (OSE) at a dose

of 400 mg $kg^{-1}$ b.wt./day. Normal rats of group 6 were intraperitoneally received saline solution and treated with OLE at a dose of 400 mg $kg^{-1}$ b.wt./day. Normal rats of group 7 were intraperitoneally injected with saline solution and supplemented orally with olive leaves extract JLE at a dose of 400 mg $kg^{-1}$ b.wt./day. Normal rats of group 8 were intraperitoneally received saline solution and exposed with OSE at a dose of 400 mg $kg^{-1}$ b.wt./day. After 5 weeks of treatment, rats were fasted for 8 h, anesthetized using diethyl ether. Blood samples were collected from orbital venous plexus in non-heparinized tubes and centrifuged at 2500 rpm for 15 min. The clear supernatants sera were frozen at -80°C till the time of various biochemical estimations including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine, blood urea nitrogen (BUN) and uric acid. All of these biochemical parameters were measured using Dimension Vista® 1500 System, USA. The level of serum glutathione (GSH) was evaluated according to the method of Beutler *et al.*[19]. The method of Nishikimi *et al.*[20] was used to determine the level of serum superoxide dismutase (SOD). The methods of Ohkawa *et al.*[21] and Aebi[22] were used to measure the levels of serum malondialdehyde (MDA) and catalase (CAT) respectively. For histopathological evaluations, liver and kidney tissues fro all experimental groups were immersed in 10% formalin, dehydrated and embedded in paraffin. After routine processing, paraffin sections were cut into 4 μm thickness, stained with hematoxylin and eosin and photographed using Motic digital microscope, Motic Company.

**Statistical analysis:** Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for Windows version 22.0 software. Data were expressed as mean±standard deviation (SD). Data were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's test. Values were considered statistically significant at $p<0.05$.

## RESULTS

The levels of serum glucose, GSH, SOD, MDA and CAT in all experimental groups were shown in Table 1. Statistically increased in the level of serum glucose were observed in diabetic rats of groups 2 ($p<0.000$), 3 ($p<0.000$), 4 ($p<0.000$) and 5 ($p<0.001$) compared with normal control rats of group 1. Statistically decreases in the level of serum glucose were noted in normal rats supplemented with OLE ($p<0.001$), JLE ($p<0.05$) and OSE ($p<0.05$). Significant decreases of serum GSH were observed in diabetic rats of groups 2 ($p<0.000$), 3 ($p<0.002$), 4 ($p<0.000$) and 5 ($p<0.005$). Diabetic rats of groups 2 ($p<0.000$), 3 ($p<0.004$), 4 ($p<0.004$) and 5 ($p<0.006$) showed statistical decline in the levels of serum SOD compared with normal control rats. In comparison with normal control rats of group 1, the levels of serum MDA were significantly elevated in diabetic rats of groups 2 ($p<0.002$), 3 ($p<0.03$), 4 ($p<0.02$) and 5 ($p<0.001$). The levels of serum CAT were significantly decreased in diabetic control rats ($p<0.000$) and diabetic rats supplemented with OLE ($p<0.02$), JLE ($p<0.005$) and OSE ($p<0.01$). Normal rats supplemented with (OLE group 6), JLE (group 7) and OSE (group 8) showed insignificant change in the levels of serum GSH, SOD, MDA and CAT.

The data in Fig. 1a-c represented the levels of serum ALT and AST and ALP. The level of serum ALT was notably increased in diabetic rats of groups 2 ($p<0.000$), 3 ($p<0.02$), 4 ($p<0.02$) and 5 ($p<0.001$) compared with normal control rats. The level of serum AST was notably increased in diabetic rats of groups 2 ($p<0.000$), 4 ($p<0.000$) and 5 ($p<0.02$), while the level of serum AST was unchanged in diabetic rats of group 3 compared with normal control rats. Statistically enhancement of serum ALP levels were observed in diabetic rats of groups 2 ($p<0.000$), 3 ($p<0.001$), 4 ($p<0.000$) and 5 ($p<0.000$) compared with normal control rats. Additionally, insignificant

Table 1: Levels of serum glucose, GSH, SOD, MDA and CAT in control, STZ, STZ plus OLE, STZ plus JLE, STZ plus OSE, OLE, JLE and OSE treated rats after 5 weeks. Percentage changes are included in parentheses

| | Parameters | | | | |
|---|---|---|---|---|---|
| Treatments | Glucose (mmol $L^{-1}$) | GSH (μmol $mL^{-1}$) | SOD (U $mL^{-1}$) | MDA (nmol $mL^{-1}$) | CAT (U $mL^{-1}$) |
| Control | 5.90±0.61 | 104.17±6.05 | 37.33±3.89 | 23.67±2.88 | 3.13±0.43 |
| STZ | 30.10±4.27[ab] (+410.2) | 62.17±7.78[ab] (-40.3) | 18.67±1.97[ab] (-50.0) | 42.00±6.57[ab] (+77.4) | 1.23±0.28[ab] (-60.7) |
| STZ+OLE | 14.73±2.85[a] (+149.7) | 84.00±9.10[a] (-19.4) | 26.50±2.67[a] (-29.0) | 32.33±5.01[a] (+36.6) | 2.33±0.44[a] (-25.6) |
| STZ+JLE | 21.53±3.97[a] (+264.9) | 74.17±5.23[a] (-28.8) | 24.15±4.66[a] (-35.3) | 35.00±4.94[a] (+47.9) | 1.87±0.25[a] (-40.3) |
| STZ+OSE | 15.35±3.01[a] (+160.2) | 78.55±9.36[a] (-24.6) | 23.33±5.05[a] (-37.5) | 33.00±4.69[a] (+39.4) | 2.27±0.46[a] (-27.5) |
| OLE | 4.70±0.37[a] (-20.3) | 105.26±12.24 (+1.1) | 35.67±3.56 (-4.5) | 21.50±2.59 (-9.2) | 3.18±0.51 (+1.6) |
| JLE | 5.28±0.34[a] (-10.5) | 107.00±4.77 (+2.7) | 36.33±3.72 (-2.7) | 21.67±2.88 (-8.5) | 3.35±0.50 (+7.0) |
| OSE | 4.73±0.26[a] (-19.8) | 104.33±6.53 (-0.2) | 35.83±5.64 (-4.0) | 21.43±2.75 (-9.5) | 3.32±0.41 (+6.1) |

Data represents the Mean±SD of 6 animals per group. [a]Indicates a significant difference between control and treated groups. [b]Indicates a significant difference between group 2 (STZ) and groups 3 (STZ+OLE), 4 (STZ+JLE), 5 (STZ+OSE), 6 (OLE), 7 (JLE) and 8 (OSE) treated rats

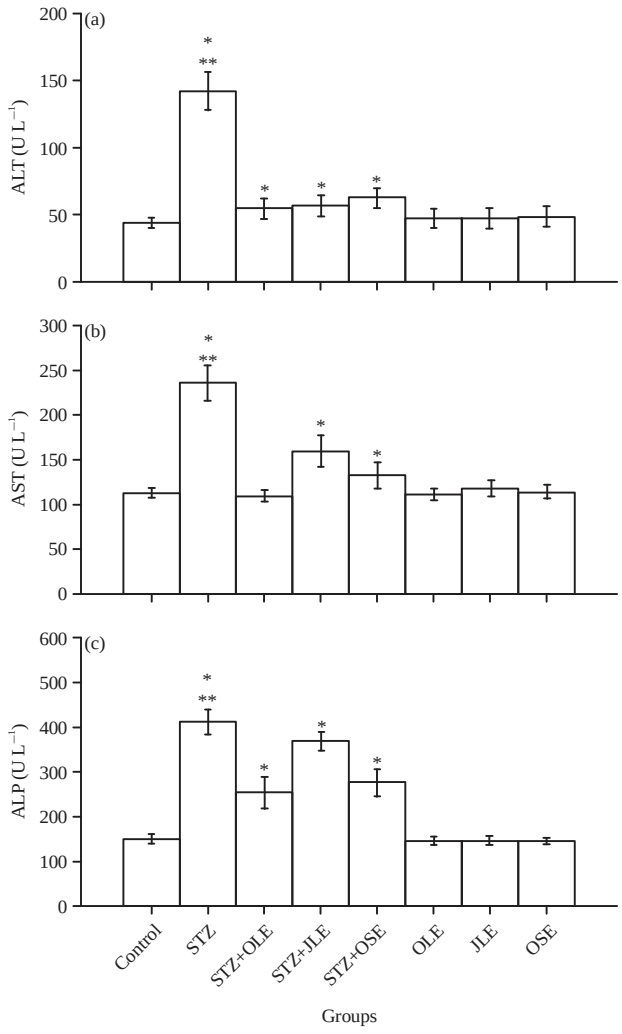


Fig. 1(a-c): Levels of serum, (a) ALT, (b) AST and (c) ALP in control, STZ, STZ plus OLE, STZ plus JLE, STZ plus OSE, OLE, JLE and OSE treated rats

*Indicates a significant difference between control and treated groups. **Indicates a significant difference between group 2 (STZ) and groups 3 (STZ+OLE), 4 (STZ+JLE), 5 (STZ+OSE), 6 (OLE), 7 (JLE) and 8 (OSE) treated rats

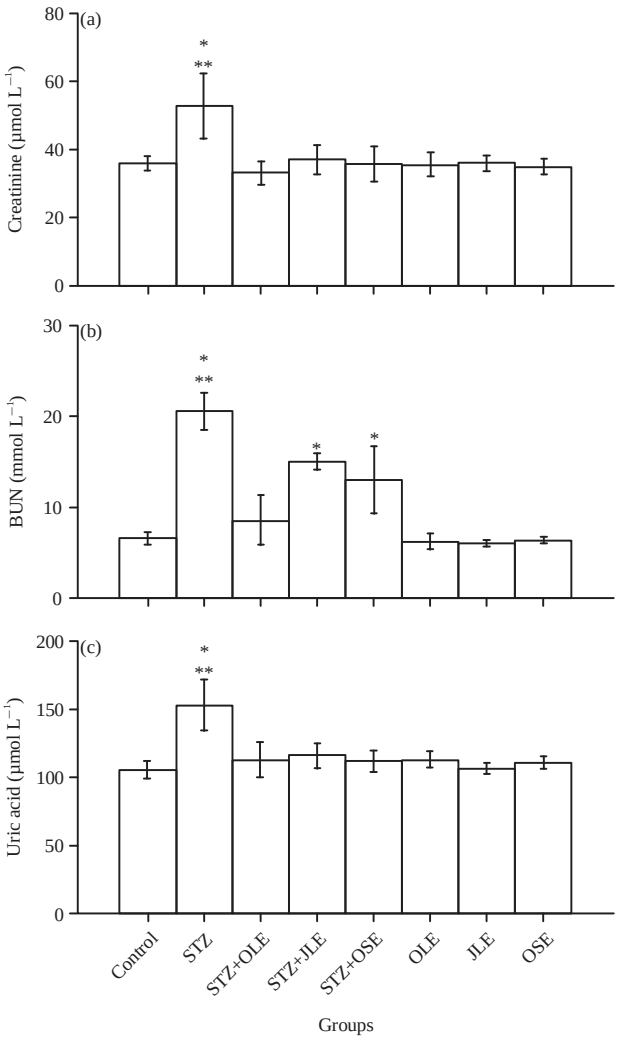


Fig. 2(a-c): Levels of serum (a) Creatinine, (b) BUN and (c) Uric acid (c) in control, STZ, STZ plus OLE, STZ plus JLE, STZ plus OSE, OLE, JLE and OSE treated rats

*Indicates a significant difference between control and treated groups. **Indicates a significant difference between group 2 (STZ) and groups 3 (STZ+OLE), 4 (STZ+JLE), 5 (STZ+OSE), 6 (OLE), 7 (JLE) and 8 (OSE) treated rats

alterations were noted in the levels of serum ALT and AST and ALP in normal rats treated with OLE (group 6), JEL (group 7) and OSE (group 8).

The levels of serum creatinine, BUN and uric acid in all experimental groups were shown in Fig. 2a-c. Notable increase in the level of serum creatinine was observed in diabetic rats of group 2 ($p<0.05$), while this parameter was notably unchanged in diabetic rats of groups 3, 4, 5 and 6 and normal rats of groups 6, 7 and 8. Noticeably increases of serum BUN were observed in diabetic rats of groups 2 ($p<0.000$), 4 ($p<0.000$) and 5 ($p<0.01$). In comparison with control group, there were no significant alterations in the levels of serum BUN in diabetic rats of group 3 and normal rats of groups 6, 7 and 8. The level of serum uric acid was significantly increased from corresponding control levels in diabetic rats of group 2 ($p<0.02$). Specifically, there were no significant differences in the levels of serum uric acid in diabetic and non diabetic rats treated with OLE, JLE and OSE.

Histopathological examination of liver tissues of normal control (group 1), diabetic control (group 2), diabetic rats supplemented with OLE (group 3), JLE (group 4) and OSE

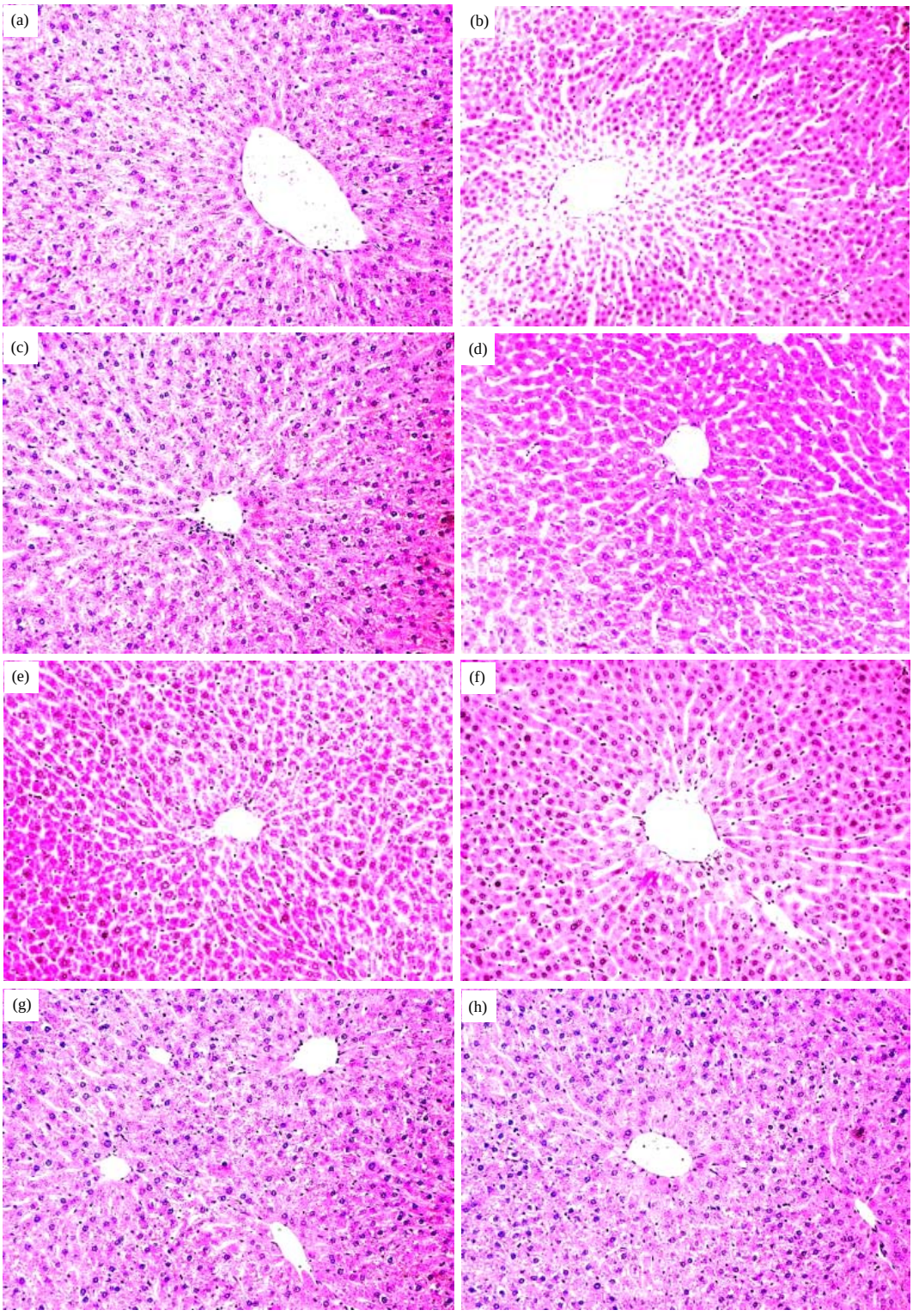


Fig. 3(a-h): Photomicrographs of liver sections in each group (a) Control, (b) STZ, (c) STZ plus OLE, (d) STZ plus JLE, (e) STZ plus OSE, (f) OLE, (g) JLE and (h) OSE treated rats. Original magnification X100

(group 5) and normal rats subjected to OLE (group 6), JLE (group 7) and OSE (group 8) are represented in Fig. 3a-h. As shown in Fig. 3a and f-h, normal liver structures including central vein, hepatic cords and liver cells were seen diabetic

rats of group 2 revealed advanced liver architecture destruction along with dis-arrangement of hepatic strands. Hepatocytes around central vein showed relatively a high number of necrosis and apoptosis. Moreover, an enlargement of the sinusoids and vacuole formations in hepatocytes were noted (Fig. 3b). Liver sections of diabetic rats of groups 4 and 5 showed mild changes including some necrosis of liver cells (Fig. 3d-e).

Results in Fig. 4 showed the renal histological structures in normal control rats (4a), diabetic control rat (Fig. 4b-d), diabetic rats supplemented with OLE (Fig. 4e), JLE (Fig. 4f) and OSE (Fig. 4g) and normal rats subjected to OLE (Fig. 4h), JLE (Fig. 4i) and OSE (Fig. 4j). Normal control rats showed a normal structure of renal cortex and medulla. Figure 4a showed the normal structure of renal (Malpighian) corpuscle. The structure of renal corpuscles in diabetic rats supplemented with OLE, JLE and OSE and normal rats subjected to OLE, JLE and OSE showed normal appearances compared with normal control rats. In diabetic control rats, there were several changes in the structure of most renal corpuscles including a degeneration of glomeruli and Bowman's capsules.

## DISCUSSION

The present investigation indicated that diabetic control rats showed significant changes in biochemical parameters. The levels of serum glucose, MDA, ALT, AST, ALP, creatinine, BUN and uric acid were significantly increased, while the levels of GSH, SOD and CAT were statistically decreased in diabetic control rats. Additionally, hepatic and renal structures revealed several alterations in diabetic control rats. ALT, AST and ALP were used as marker enzymes to assess the extent of liver damage[23,24], while creatinine, BUN and uric acid served as a kidney injury biomarkers[25,26]. The present biochemical and histopathological alterations in diabetic control rats are in agreement with different previous studies which indicated that the exposure to STZ led to induce severe physiological and biochemical disturbances and histopathological changes in diabetic animals[27-30]. The present hepatorenal damage was caused by oxidative damage which indicated by the measurement of serum GSH, SOD, MDA and cat levels. The generation of reactive oxygen species (ROS) due to prolonged hyperglycemia caused oxidative injury of tissues and organs and diabetic complications. However, these processes lead to diabetic complication which associated with increase of morbidity and mortality[31,32]. The DM plays a central role in the initiation and progression of liver injury and this progressive disease is an independent risk factor for the development of chronic liver diseases[33]. Degenerative changes and damage of liver were attributed to enhancement of lipid peroxidation in chronic DM cases[34,35]. Several studies demonstrated that the levels of serum GSH, SOD and CAT were declined in diabetic animals[27,36,37]. Moreover, various investigations showed that the level of MDA was elevated both in serum and kidney tissues and the levels of anti-oxidant enzyme were decreased in renal homogenates of diabetic rats[38-40].

The present study showed that the administration of OLE, JLE and OSE can prevent severe alterations of biochemical parameters and disruptions of liver and kidney structures in diabetic rats. The present study revealed that the studied extracts showing protective role for diabetic hyperglycemia, hepatopathy and nephropathy and improved the oxidative markers by minimizing the oxidative stress. The control of glucose, using of anti-oxidants and management of DM inhibit the activation of oxidative stress and the progression of diabetic complications. Currently, biologically active substances, especially antioxidants with plant origin have been devoted to the main branch of modern medical therapy. The anti-oxidant and phenolic compounds (e.g., tyrosol, oleuropein and hydroxytyrosol) were considered as bioactive factors of olive tree extracts. Oleuropein is a phenolic compound from secoiridoids family isolated from olive leaves almost a century ago[41,42]. Oleuropein has been related to improved glucose metabolism. Moreover, the anti-hyperglycemic influence of oleuropein was reported in diabetic animals. Murotomi *et al.*[43] showed that the oleuropein attenuated hyperglycemia and impaired glucose tolerance and reduced oxidative stress in diabetic mice. The phytochemical screening of successive extracts of *Juniperus* plants revealed the presence of alkaloids, saponins, resins, flavonoids, tannins and phenols[44]. The first isolated compound from *J. procera* leaves was identified as 3, 4, 3, 7-tetrahydroxyflavone[45]. The new flavonoid was identified as: 4H-1-Benzopyran-4-one-7-[[6-O-(6-deoxy-alpha-L-mannopyranosyl)-beta-D-glucopyranosyl] deoxy]-2,3-dihydr-5-hydroxy-2-(3-hydroxy-4-methoxy-phenyl)[46]. The influence of leaves extract of *J. phoenicea* was examined in STZ-diabetic rats. In diabetic rats treated with *J. phoenicea* leaves extract, the levels of serum blood glucose and MDA was significantly declined, while the levels of serum insulin, GSH and SOD were statistically increased compared with diabetic control rats. Furthermore, treatment with *J. phoenicea* leaves extract improved lipid profile and normalized serum levels of liver enzymes and kidney function parameters[47]. *O. ficus-indica* cladodes contain significant amount of polyphenols and tocopherols that are effective radical scavengers. Previous studies showed that the fruits and stems

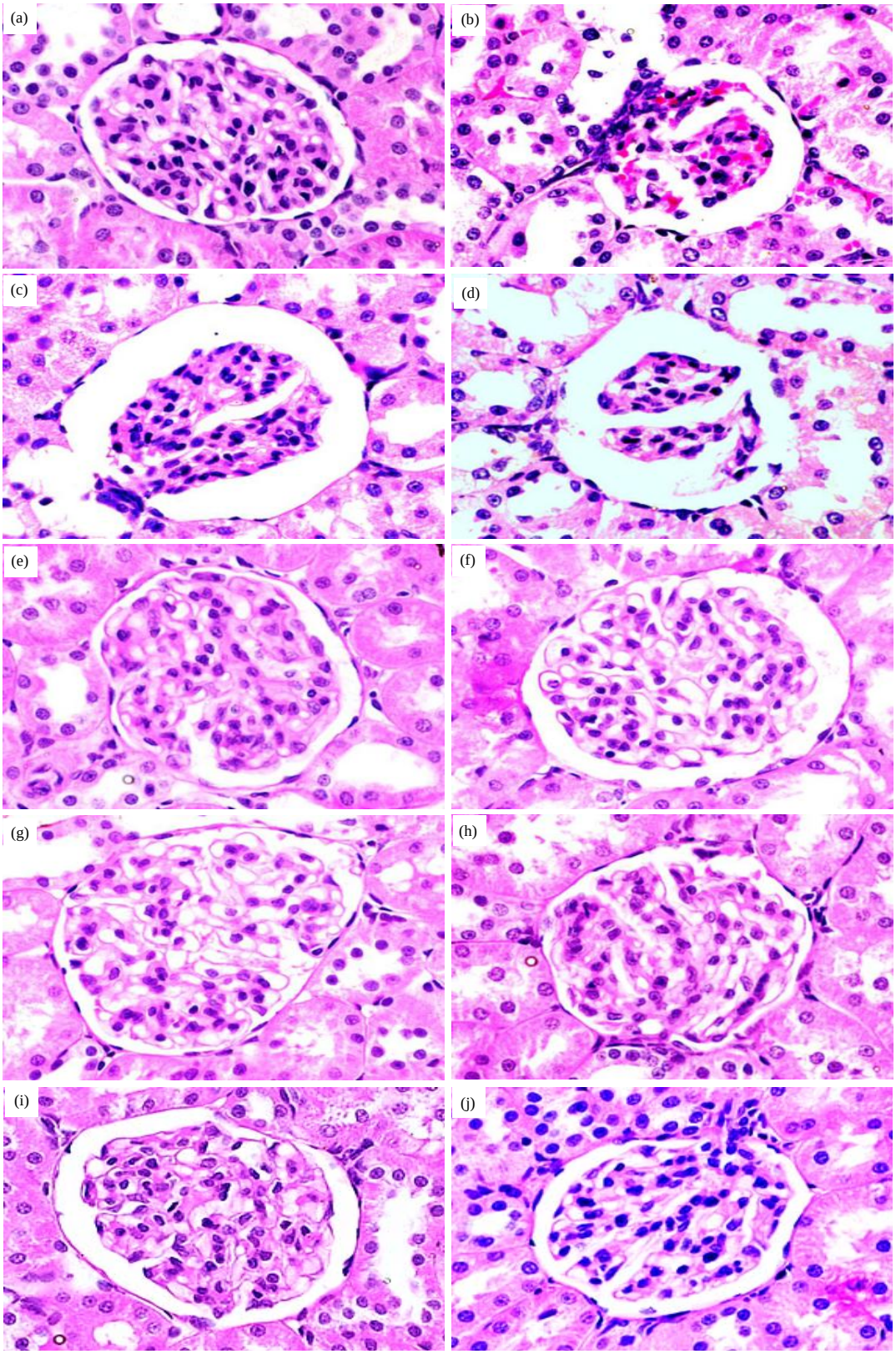


Fig. 4 (a-j): Photomicrographs of renal corpuscle in each group (a) Control, (b-d) STZ, (e) STZ plus OLE, (f) STZ plus JLE, (g) STZ plus OSE, (h) OLE, (i) JLE and (j) OSE treated rats. Original magnification X400

of *O. ficus-indica* exhibited hypoglycemic influences in STZ diabetic rats[48,49]. Abd El-Razek and Hassan[50] evaluated the effect of *O. ficus-indica* fruit on diabetic rats. They showed that fruit juice has a strong anti-oxidant property and can scavenge ROS which indicated by the decline of blood glucose, cholesterol and MDA levels and the improvement of the levels of ALT, AST, ALP, GSH and SOD. However, in view of the present findings, this study compares for the first time the effect of these plant extracts on hyperglycemia and hepatorenal injury. Treatment with these extracts cause attenuation of biochemical and histopathological alterations in diabetic rats. These results supported the importance of blood glucose control and protection of hepatorenal injury. Finally, long period investigations on the effects of these extracts on chronic diabetes are required to develop a successful and potent therapy.

## CONCLUSION

The present study provided evidence indicating that the studied extracts significantly improved the levels of glucose, oxidative stress parameters, liver and kidney biochemical markers as will as the histopathological alterations in STZ diabetic rats. It is obviously that the hepatorenal protective effects of these extracts strongly related to the suppression of oxidative stress associated with DM. Additional studies are required to isolate and identify the active constituents of these extracts as hypoglycemic factors.

## SIGNIFICANCE STATEMENT

The present study compares the hepatorenal protective effects of *O. oleaster* and *J. procera* leaves and *O. ficus-indica* stems extracts on DM induced by STZ in male rats. The results of this study will add significant understanding to the body of knowledge of the effect of these plant extracts as hypoglycemic agents and thus this study opens up new areas of scientific investigations in the fields of biomedical science.

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