The possible therapeutic effect of ethanolic olive leaves extract or bone marrow mesenchymal stem cells on kidney of gamma irradiated adult male rats

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Abstract: Exposure to doses of ionizing radiation is associated with physiopathological and histopathological changes. These changes differ in their severity according to the radiosensitivity and responses of individual organs and tissue. The aim of this study was to elucidate the possible therapeutic effect of ethanolic olive leaves extract (OLE) or bone marrow mesenchymal stem cells (BM-MSCs) on kidney of irradiated adult male rats using biochemical parameters, histopathology and quantitative histochemistry. **Matrerial and methods**- 60 adult male albino rats (Sprague dawely strain) were used in this study. They were divided into 5 groups (C group: untreated control rats; R group: rats exposed to a single dose of gamma-radiation (3 Gy); OLE group: rats were treated with olive leaves extract (15 mg /kg body weight/day for 30 days); R+OLE group: rats of this group were treated with olive extract 15 mg /kg body weight/day for 30 days after irradiation; R+MSCs group: rats of this group were irradiated with 3Gy then injected with bone marrow mesenchymal stem cells (BMSCs) 1×10^6 cells/500µL suspension through caudal vein about 6h post radiation exposure. The experimental rats were sacrificed on the 7th and 30th day post irradiation, except **R+MSCs** group were sacrificed only on the 30th day post exposed to radiation. **Results**- Rats exposed to gamma radiation showed many biochemical changes which included a significant increase in serum urea, creatinine and kidney MDA level while, kidney GSH level showed a significant decrease. Many histopathological lesions were observed in the kidney tissue, congested, lobulated and atrophied glomeruli with wide Bowman spaces, most tubules were dilated, cellular detachment, pyknotic nuclei, intratubular leukocytic infiltration, edema and thickening of atrial wall. In addition, irradiated group showed a significant increase in collagen and amyloids, while a significant decrease in PAS+ve materials, total protein and total DNA content was detected. **Conclusion**- From the biochemical, histopathological and histochemical studies, ethanolic olive leaves extract and mesenchymal stem cells ameliorated the induced kidney tissue damage of the irradiated group. MSCs proved to have more powerful therapeutic effect than that observed by OLE.
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Key words: Gamma radiation - Albino rats -Kidney- Ethanolic olive leaves extract (OLE) - Bone marrow mesenchymal stem cells (BMSCs).

1. Introduction

The effects of ionizing radiation on biological systems was mainly generated from experimental studies on animals and the radiation accidents. These effects depend on many factors as radiation type, radiation dose, type and radio sensitivity of the tissue receiving the radiation, volume of tissue exposed and also the type of exposure **(El-Naggar, 2009).**

Oxidative stress occurs when there is excessive free radical production and/or low antioxidant defense and results in chemical alterations of biomolecules causing structural and functional modifications. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are products of normal cellular metabolism (**Valko *et al*., 2007**).

Mohamed *et al*. (2015) revealed that irradiation of rats caused significant elevation in serum urea and creatinine, propagation in lipid peroxidation (MDA), elevation in nitric oxide (NO) concentration and decline in reduced glutathione (GSH) content. Moreover, histopathological examination of kidney tissue reflected marked injury.

In order to overcome the potential harmful effect of free radicals and to reduce the damage by oxidants, a variety of synthetic antioxidants have been examined. However, the uses of synthetic compounds are restricted because of their toxic or carcinogenic effects **(Pokorny, 1991).** Natural antioxidants, particularly those containing phenolic components, are of considerable interest as dietary supplements or food preservatives **(Halliwell, 1995).**

Olive leaf extract (OLE) is derived from the olive leaves. It was used by the ancient Egyptian and Mediterranean cultures to treat a variety of health conditions, including infections, fever and pain **(Omar, 2010).** The main constituent of the olive leaves is oleuropein, one of iridoide monoterpenes, which is thought to be responsible for

pharmacological effects. Furthermore, the olive leaves contain triterpenes (oleanolic and maslinic acid), flavonoids (e.g., luteolin, apigenine and rutin) and chalcones such as olivin, olivin-diglucoside (**Meirinhos *et al*., 2005; Pereira *et al.*, 2007**).

Bashandy *et al.* (2014) reported that radioprotective and radio-therapeutic effects against whole body gamma radiation by preventing oxidative stress through ROS scavenger showed by OLE confirms the importance of flavonoids and substituted phenol present in its composition**.**

Prevention of free radical formation by oleuropein occurs through its ability to chelate metal ions, such as Cu and Fe, which catalyze free radical generation reactions and through its inhibitory effect on several inflammatory enzymes like lipoxygenases **(Andrikopoulos *et al*., 2002).**

Stem cell is undifferentiated cell with the capacity for multi lineage differentiation and self-renewal without senescence. **(Orbay *et al*., 2012).** Stem cell therapies are a category of regenerative medicine, the promise of which includes innovative therapies for organ failure and degenerative diseases.

Mesenchymal stem cells (MSCs) have been isolated from several adults and fetal tissues. Currently, BM is considered the most reliable source of MSCs for adults. From this tissue, MSCs can be isolated in high numbers after the separation and culture of the mononuclear fraction of BM cells **(Insausti *et al*., 2012).**

MSC treatment can control the antioxidant/oxidant balance after kidney injury (**DeAlmeida *et al*., 2013**).

Weissman (2000) reported that stem cell therapy holds a great promise for the repair of injured tissues and organs, including kidney. There has been considerable focus on the ability of stem cells to differentiate into non-haemato-poietic cells of various tissue lineages, including cells of kidney**.** This growing evidence has led to a reconsideration of the source of cells contributing to renal repair following injury **(Oswald *et al*., 2004).** In addition, **Zahkouk *et al*. (2015**) stated that mesenchymal stem cells caused a significant improvement in kidney functions as well as renal tissues in cisplatin induced renal failure in adult male rats.

2 Materials and Methods

Experimental animals, feeding and maintenance

A total of 60 male Swiss albino rats (Sprague Dawely strain), weighing 120-130 gm, were obtained from Holding Company for Biological products & Vaccines (**Vacsera**), Helwan, Egypt. All animals were kept for about 15 days, before the onest of the experiment, under observation to exclude any intercurrent infection and to acclimatize the laboratory conditions. The animals were kept in metal cage with good aerated covers at normal atmospheric temperature (25+5ºc) and at normal daily 12 hrs dark/light cycles in the experimental animal unit, Zoology Department, Faculty of Science (Boys), Al Azhar University. They were fed commercial food pellets and provided with tap water a*d libitum*. All experiments took place in the laboratories of the Center of Genetic Engineering, Faculty of Science (Boys), Al Azhar University, Cairo.

Gamma-irradiation procedure

Irradiation process was performed using Gamma Cell-40 achieved by Egypt's National Center for Radiation Research and Technology (NCRRT), Cairo.

The dose rate was 0.5 Gy/min at the time of the experiment.

Olive leaves (*olea europaea*) extraction

Olive leaves were weighed and ground to a fine powder in an electric mixer. The powdered plant material was extracted in70% ethanol by soxhlet apparatus for 10 hours continuously **(Mohammadi and Naik, 2008; Abo Ghanema and Sadek, 2012).** The extract was administrated daily at dose 15mg/kg b. w. for 30 days by ingastric gavages according to the method of **Alirezaei *et al*. (2012**).

Mesenchymal stem cells (MSCs) transplantation

MSCs cells concentration for transplantation was 1×10^6cells/500µL suspension transplanted into the irradiated rats through caudal vein according to **Shaohua and Dongcheng (2013).** A total of ten animals received the 500 µL cell suspension.

Experimental design

The experimental animals were divided into 5 groups.

Group 1: control rats **(C)**

Group 2: irradiated **(R):** animals were exposed to single dose (3Gy) of whole body γ-radiation.

Group 3: olive leaves extract **(OLE):** 15 mg extracted olive leaves /kg body weight was administrated daily for 30 days.

Group 4: olive irradiated **(R+OLE)**: animals were exposed to 3 Gy of γ- radiation and then treated with olive leaves extract for 30 days.

Group 5: mesenchymal stem cells irradiated **(R+MSCs):** animals were exposed to 3Gy as a single dose of gamma-radiation and then injected with MSCs (1×10^6 cells/500µL suspension) through the caudal vein.

All experimental rats were sacrificed at 7 and 30 days post irradiation, except **R+MSCs** group which was sacrificed only after 30 days of irradiation.

Blood sample collection:

At the end of the experimental period, the overnight fasted animals (12- 16h) were sacrificed under diethyl ether anesthesia. Blood samples were taken from orbital vein and centrifuged at 3000 rpm

for 10 min. The clear non-hemolysed supernatant sera was quickly removed and immediately stored at -20°C untill used for further analysis of biochemical parameters.

Tissue sampling

After blood collection, the animals were rapidly sacrificed and the right and left kidney (both kidneys) of each animal were removed, one kidney was fixed in10% buffered formalin solution for histological and histochemical studies and the other was washed with saline, dried, rolled in a plastic sack of aluminum foil and stored at -20^{o}C until homogenization for tissue biochemical analysis (MDA and GSH).

Kidney homogenate

1gm wet weight of kidney was homogenized in 10 ml of distilled water (10% tissue homogenate), then the homogenates were centrifuged at 7000 rpm for 20 minutes and clear supernatants were drawn out and divided into aliquots and stored at -20^{o}C till the determination of the requested biochemical analysis.

Biochemical analyses

Serum urea concentrations were determined colorimetrically as described by **Patton and Crouch (1977)**. Serum creatinine concentrations were determined colorimetrically as described by **Kroll *et al*. (1987).**

The tissue glutathione (GSH) content was determined according to the method of **Beutler *et al.* (1963).** Tissue malondialdehyde (MDA) level was determined according to the method of **Yoshioka *et al.* (1979).**

Histological and histochemical techniques

The animals were sacrificed at 7 and 30 days post irradiation, then kidney was immediately excised and fixed in 10% neutral formalin for 24hours followed by dehydration in ascending grades of alcohol, clearing in xylene and embedded in paraffin wax. Sections were then cut at 5µ thickness and stained by hematoxylin and eosin stain for histopathological study **(Bancroft and Gamble, 2002).** Collagen fibers were stained by Mallory's trichrome stain **(Pears, 1977).** Polysaccharides were stained by periodic acid Schiff's (PAS) reagent **(Drury and Wallington, 1980).** Total proteins were stained by mercuric bromophenol blue method **(Mazia *et al.,* 1953).** DNA was stained by Feulgen reaction **(Drury and Wallington, 1980**). Amyloid-β protein was stained by Congo red technique **(Valle, 1986).**

Quantitative morphometric analysis

The optical density of histochemical stained sections in kidney cortex for carbohydrates, total protein, DNA and Amyloid-β protein of the control and treated groups was recorded using IPWIN 32 image analysis software.

Statistical analysis

Statistical analyses were performed using analyses of variance (ANOVA) according to **Snedecor and Cochran (1980).** The data were processed and analyzed using the SPSS software (Statistical Analysis for Social Science, Version 8). Significant differences between treatment means were determined by student t-test. Data were presented as mean ± SE and $P \leq 0.05$ was considered statistically significant.

3. Results

Biochemical parameters

Serum urea and creatinine levels were measured in all groups. In irradiated group radiation induced a significant increase in serum urea and creatinine throughout the experimental periods when compared to the control group. Meanwhile, treatment with OLE alone induced a non- significant change in urea and creatinine throughout the experimental periods.

However, after OLE administration to irradiated animals the level of urea and creatinine showed a significant increase after 7 days post irradiation compared to the control and a significant decrease in comparison with the irradiated group. While, after 30 days of irradiation a non-significant change was observed in R+OLE and R+MSCs groups in comparison with the control and a significant decrease in comparison with the irradiated group (Figs.1&2).

The data presented in figs. 3&4: indicated that the irradiated rats exhibited a significant increase in malondialdehyde (MDA) levels and a significant decrease in glutathione (GSH) content as compared to the control group. Treatment with OLE alone induced a non-significant increase in MDA and GSH level after7 and 30days post treatment. Irradiated rats treated with OLE showed a significant increase in MDA levels after 7days of irradiation and a non-significant increase after 30 days of irradiation in comparison with the control while, in comparison with the irradiated group MDA level showed a significant decrease throughout the two experimental periods.

GSH level in irradiated rats treated with OLE showed a significant decrease after 7 days of irradiation and a non-significant decrease after 30 days compared to the control while GSH level recorded a significant increase during the experimental period when compared to the irradiated group. Meanwhile, irradiated rats treated with MSCs showed a non-significant change in MDA and GSH level after 30 days of irradiation as compared to the control group. While, in comparison with the irradiated group MDA level showed a significant decrease and GSH showed a significant increase after 30 days of irradiation.

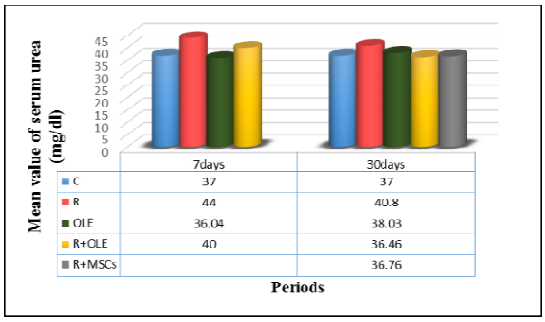


Fig. 1: the mean value of serum urea (mg/dl) in irradiated rats after treatment with OLE or MSCs.

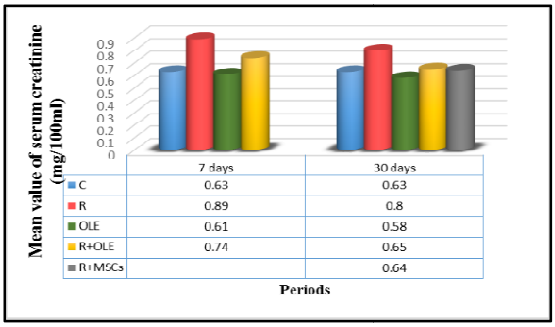


Fig. 2: the mean value of serum creatinine (mg/100ml) in irradiated rats after treatment with OLE or MSCs.

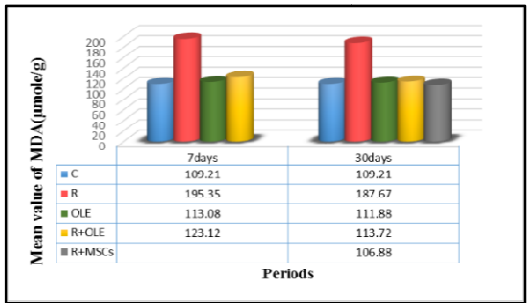


Fig. 3: the mean value of kidney tissue malondialdehyde (MDA)(µmole/g) level in irradiated rats after treatment with OLE or MSCs.

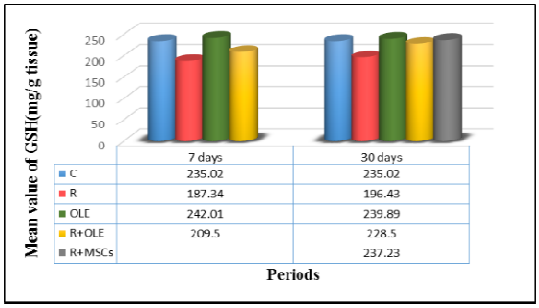


Fig. 4: the mean value of kidney tissue glutathione (GSH) (mg/g tissue) level in irradiated rats after treatment with OLE or MSCs.

Histopathological observations of kidney

Control group (C): figs. 5&6 showed the normal structure of kidney cortex. The normal distribution of collagen is demonstrated in fig. 19**.**

Irradiated group (R): 7 days after irradiation showed many deleterious changes in kidney cortex included congested, lobulated and atrophied glomeruli with wide empty spaces, most tubules lost their normal architecture, numerous intertubular hemorrhagic areas, cellular debris, pyknotic nuclei, cellular detachment, intertubular leukocytic infiltration, edema between renal tubules and thickening of atrial wall. Some of the convoluted tubules showed hydropic degeneration and cloudy swelling with faint staining affinity, poorly detected brush borders of the proximal convoluted tubules (Figs. 7-10).

While, kidney of animals excised after 30 days were atrophied, congested, also exhibited hypercellularity glomeruli, wide Bowman's spaces, intertubular hemorrhagic areas, thickening of atrial wall, intertubular leukocytic infiltration and prominent signs of degeneration in some epithelial cells of the distal convoluted tubules (Figs.11-13).

Using Mallory's trichrome stain showed highly increased collagen fibers in kidney cortex especially in the brush borders and in the basement membranes of the convoluted tubules and in Bowman's capsules (Figs. 20&21) after 7 and 30 days respectively.

Olive leaves extract treated group (OLE): sections from animals drenched olive leave extract showed more or less like normal appearance of the glomerulus, proximal and distal convoluted tubules (Figs. 14 & 15) after 7and 30 days of treatment respectively.

OLE group showed almost moderately stained and normal distribution of collagen fibers in kidney cortex (Figs. 22&23) after 7 and 30 days of treatment respectively.

Olive irradiated group (R+OLE):

this group showed normal appearance of the glomerulus, proximal and distal convoluted tubule, while some pyknotic nuclei and cellular debris in the tubular lumen of some tubules were still detected after 7 days of irradiation (Fig. 16). After 30days well-developed kidney architecture was observed with some pyknotic nuclei (Fig. 17). Almost normal collagen fibers distribution was obvious in Bowman's capsules, glomeruli and brush borders of the proximal convoluted tubules (Figs. 24&25) after 7 and 30 days of irradiation respectively.

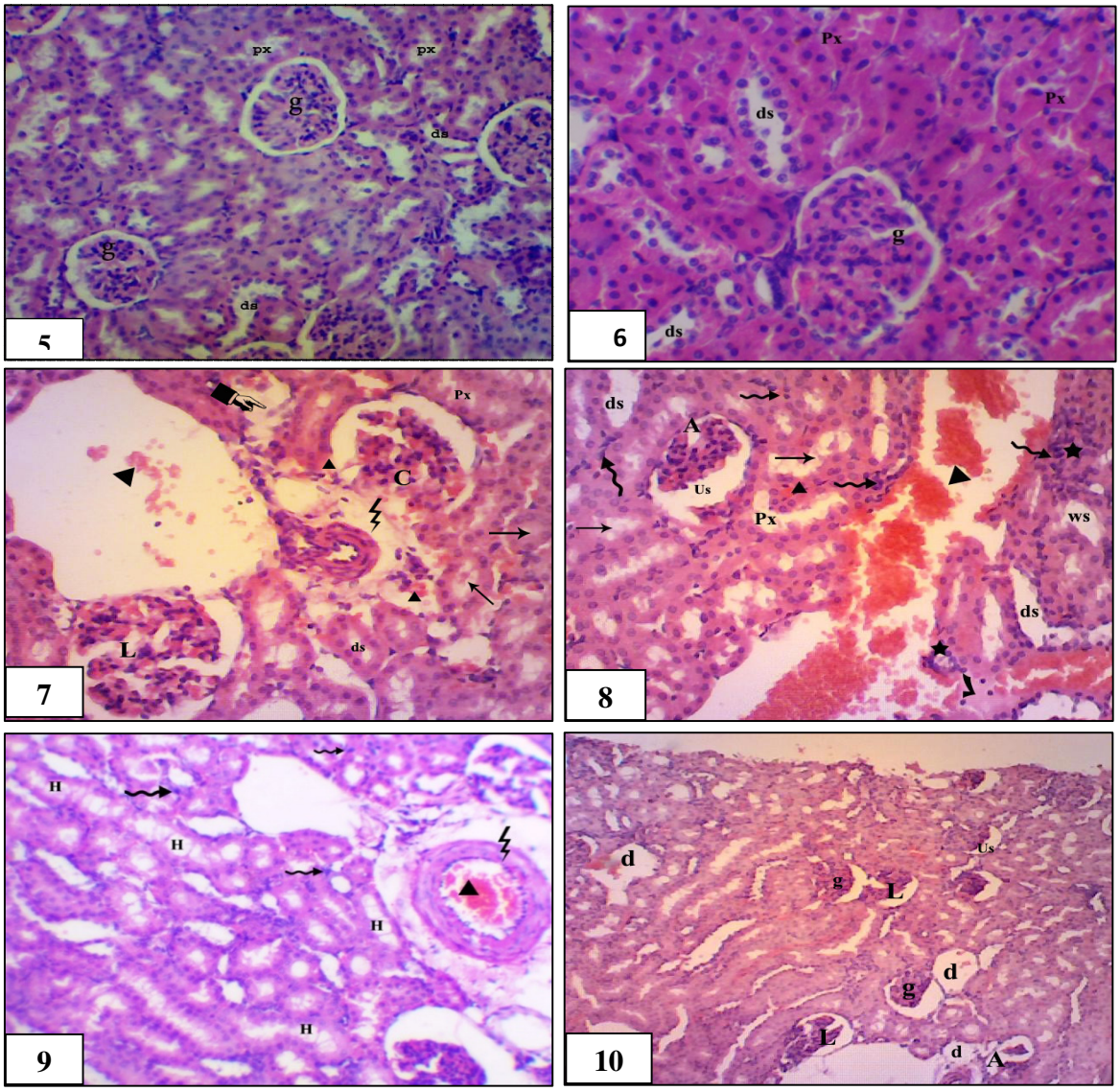
Stem cells irradiated group (R+MSCs):

this group showed well developed kidney architecture, the glomerulus, proximal and distal convoluted tubules appeared more or less normal with some pyknotic nuclei and few debris in their lumen (Fig. 18). Mallory's trichrome stain recorded normal distribution of collagen fibers in glomeruli, distal

convoluted tubules and brush borders of the proximal convoluted tubules after 30 days of γ-irradiation (Fig. 26).

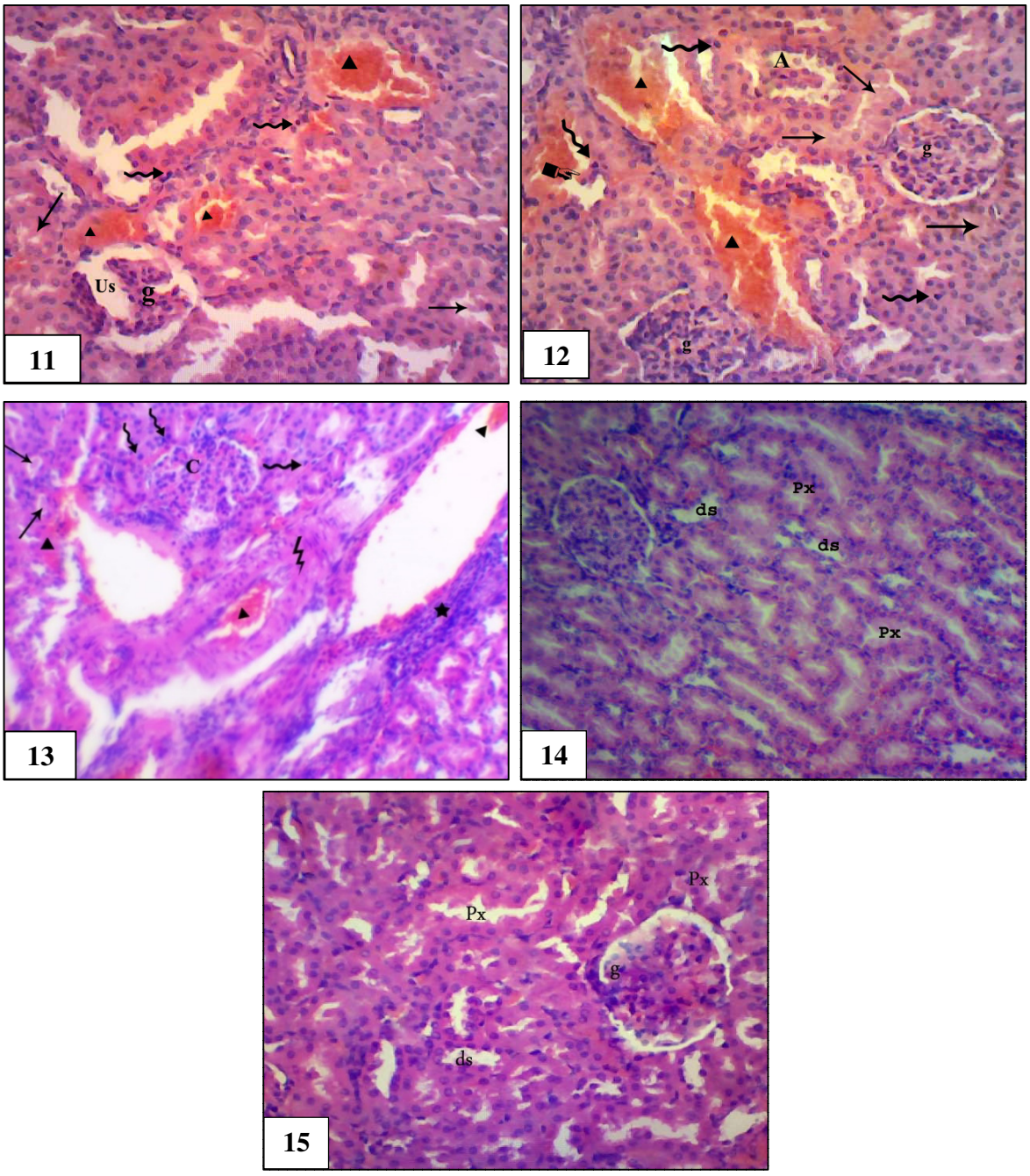
Quantitative histochemical measurements

Irradiated rats **(R)** exhibited a significant decreased in the mean value of PAS +ve materials, total protein and total DNA content of kidney cortex after 7 and 30 days of irradiation while a significant increase in amyloid β-protein content was recorded during the experimental periods. on the other hand, rats administrated olive leaves extract (OLE) alone or after irradiation and those injected with mesenchymal stem cells (MSCs)post exposed to radiation showed a non-significant change in the mean value of PAS +ve materials, total protein, total DNA and amyloid β-protein content of kidney cortex throughout the experimental periods when compared to the control rats.



Figures 5-10: photomicrographs of sections in kidney cortex of the control and treated groups. (H&E X100**,50&**200).**Figs. 5&6: sections in kidney cortex of the control rats showing** normal glomeruli (**g**), proximal (**px**) and distal (**ds**) convoluted tubules. **(5X 100&6 X 200).**

Figs. 7-10: sections in kidney cortex of the irradiated rats after 7 days of irradiation(R) showing: congested (**C**) glomeruli, numerous hemorrhagic areas (►), cellular detachment (**hand**), thickening of atrial wall (**corrugated line**), edema between renal tubules **(check mark)**, intertubular leukocytic infiltration (**star**) and cellular debris (→) in lumen of some renal tubules, most tubules are dilated, their cells have pyknotic nuclei (**corrugated arrow**), hydropic degeneration in the lumen of renal tubules **(H),** many of the glomerular tuft (**g**) are lobulated (**L**) or atrophied (**A**) with wide urinary space (**Us**) and some are totally degenerated (**d**). **(7 X 200, 8 & 9 X 100 &10 X 50).**

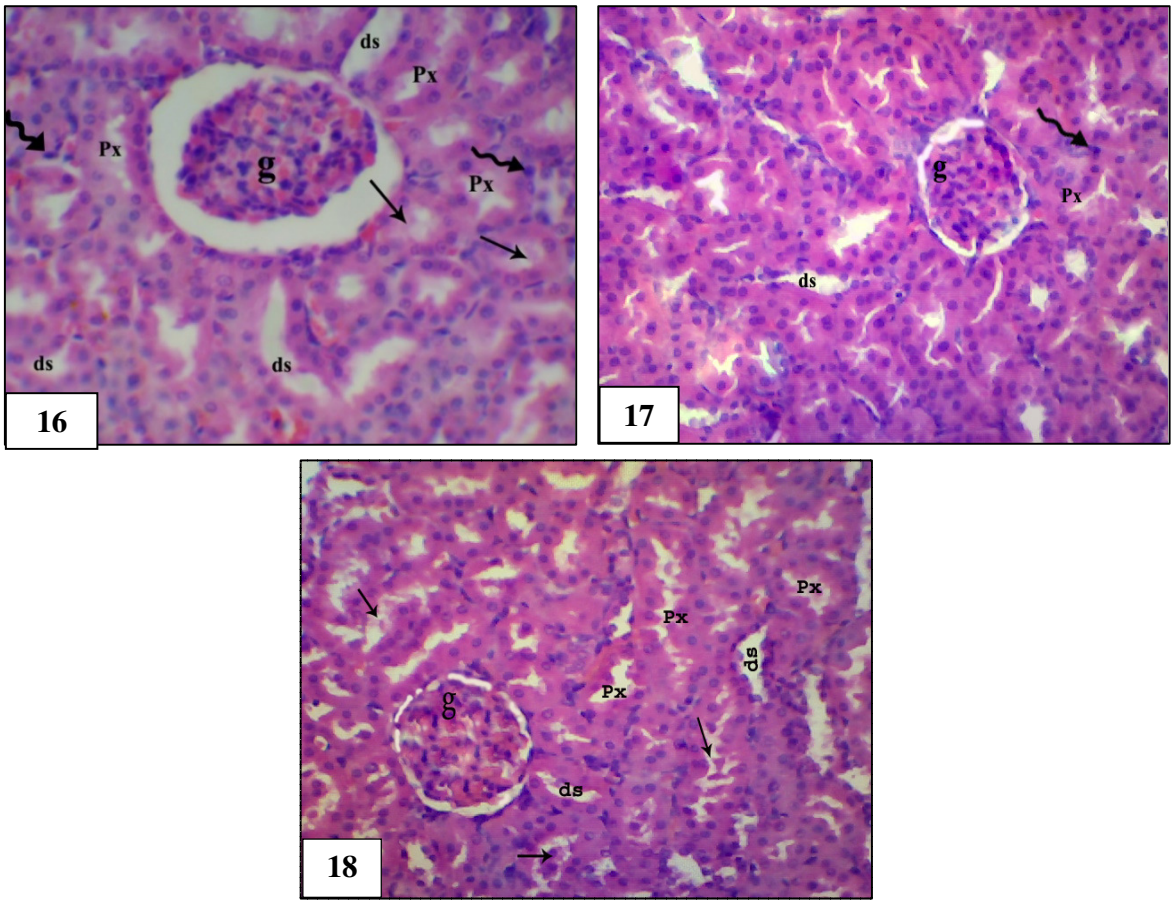


Figs 11-15:

Figs. 11-13: sections in kidney cortex of the irradiated rats after 30 days of irradiation (R) showing most tubules lost their normal architecture, numerous degenerated tubules, congested and lobulated glomerulus(**g**) with wide urinary space, atrophied **(A),** congested **(C)** and hypercellularity glomeruli **(g)**, prominent internal hemorrhagic area (►), pyknotic nuclei in the cells of tubules (**corrugated arrow**) with cellular debris in the lumen of most tubules(►), cellular detachment of the tubular cells (**hand**), congested artery with thickened wall (**corrugated line**) and intertubular leukocytic infiltration(**star**).**(11, 12 & 13** H&E **X 100).**

Fig. 14: sections in kidney cortex of OLEgroup after 7 days of treatment showing the glomerulus (**g**), proximal (**Px**) and distal (**ds**) convoluted tubules which appear more or less normal. (H&E **X 100).**

Fig. 15: sections in kidney cortex of OLE group after 30 days of treatment showing the glomerulus (**g**), proximal (**Px**) and distal (**ds**) convoluted tubules which appear more or less normal. (H&E **X 100).**

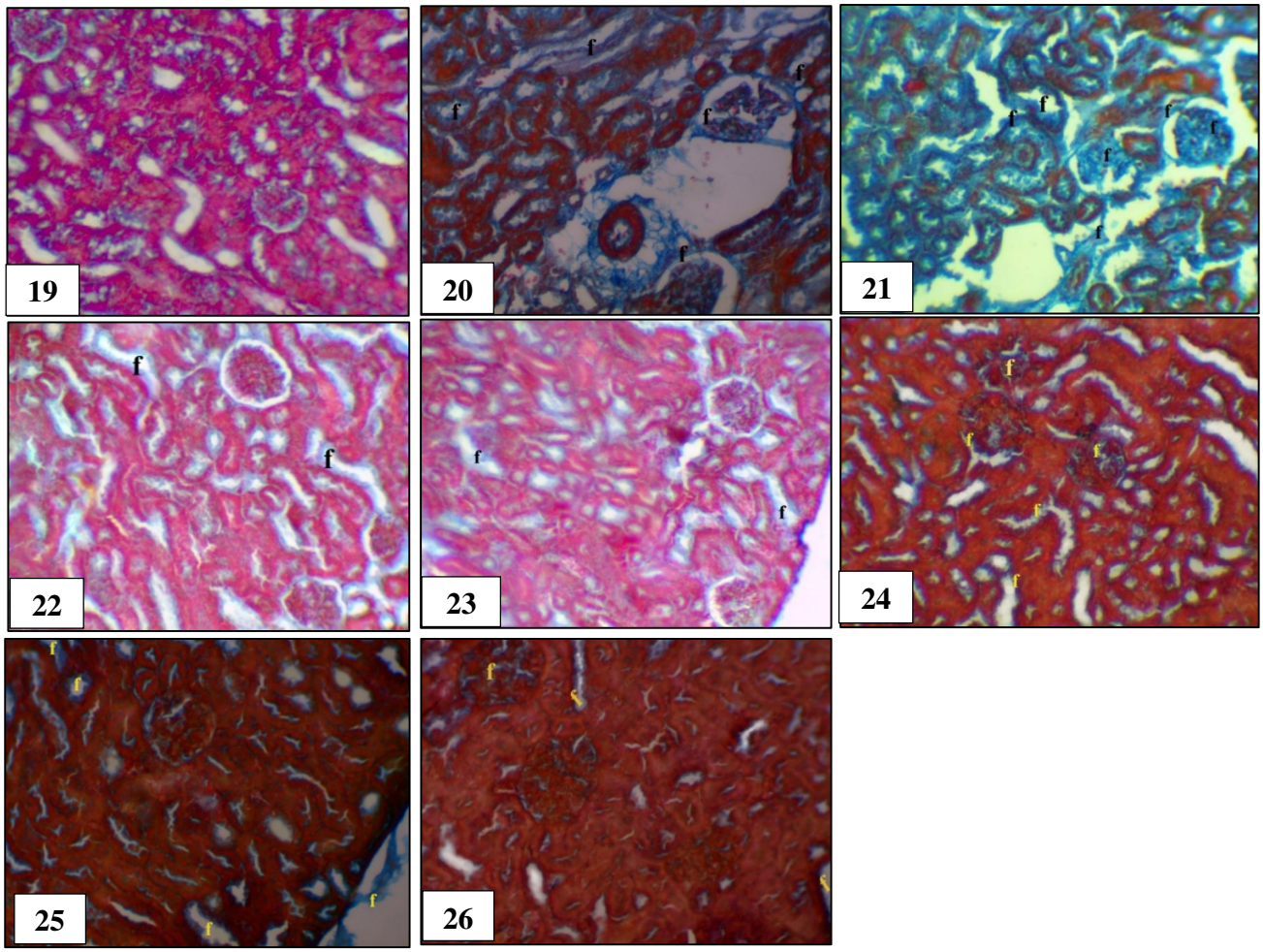


Figs 16-18:

Fig. 16: **sections in kidney cortex of R+OLE group after 7 days of irradiation showing** normal appearance of the glomerulus (**g**), proximal (**px**) and distal (ds) convoluted tubules, while some pyknotic nuclei (**corrugated arrow**) and cellular debris (⟶) in the tubular lumen of some tubules were still detected. (H&E **X 200).**

Fig. 17: sections in kidney cortex of R+OLE group after 30 days of irradiation showing well developed kidney architecture, the glomerulus (**g**), proximal (**px**) and distal (**ds**) convoluted tubules appeared more or less like normal while some pyknotic nuclei (**Corrugated arrow**) were still detected. (H&E **X 100).**

Fig. 18: sections in kidney cortex of R+MSCs group showing well developed kidney architecture, the glomerulus (**g**), proximal (**Px**) and distal (**ds**) convoluted tubules appeared more or less normal with some pyknotic nuclei (**Corrugated arrow**) and few debris (⟶) in their lumen. (H&E **X 100).**



Figs. 19-26: photomicrographs of sections in kidney cortex of the control and treated groups representing distribution of collagen fibers: (Mallory's trichrome stain X 100&200).

Fig. 19: sections in kidney cortex of the control rat showing normal distribution of collagen fibers. Notice: thin collagen bundles supporting the Bowman's capsules and walls of the proximal and distal convoluted tubules. (X100).

Fig. 20: sections in kidney cortex of the irradiated rats after 7 days showing highly increased collagen fibers **(f)** in kidney cortex especially in the brush borders and in the basement membranes of the convoluted tubules and in Bowman's capsules. (X200).

Fig. 21: sections in kidney cortex of the irradiated rats after 30 days showing intensely stained collagen fibers **(f)** in kidney cortex most of the tubules and glomeruli are replaced by collagen fibers. (X100).

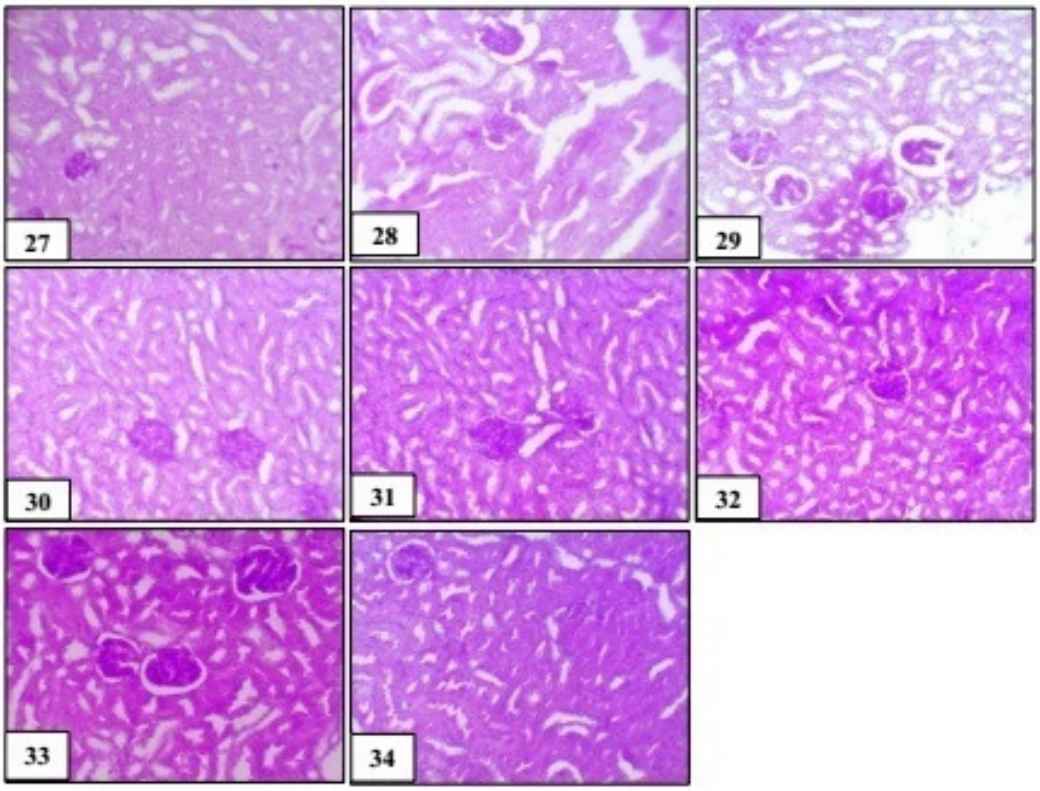
Fig. 22: sections in kidney cortex of OLE group after 7 days showing almost moderately stained and normal distribution of collagen fibers **(f)** in kidney cortex.(X100).

Fig. 23: sections in kidney cortex of group OLE after 30 days showing almost normal collagen fibers **(f)** distribution in Bowman's capsules, glomeruli and brush borders of the proximal convoluted tubules. (X100).

Fig. 24: sections in kidney cortex of the irradiated rats treated with OLE after 7 days showing almost normal collagen fibers **(f)** distribution in Bowman's capsules, glomeruli and brush borders of the proximal convoluted tubules. (X100).

Fig. 25: sections in kidney cortex of the irradiated rats treated with OLE after 30 days showing almost normal distribution of collagen fibers **(f)** with moderate staining in kidney cortex. (X100).

Fig. 26: sections in kidney cortex of the irradiated rats treated with MSCs after 30 days showing normal distribution and faintly stained collagen fibers **(f)** distribution in glomeruli, distal convoluted tubules and brush borders of the proximal convoluted tubules. (X100).



Figs. 27-34: photomicrographs showing distribution of PAS +ve materials in kidney cortex of the control and treated groups after 7 and 30 days of irradiation (PAS X 100).
Fig. 27: kidney cortex of a control rat showing moderately stained PAS +ve materials in the basement membranes, glomerular capillaries and brush borders of the proximal convoluted tubules with some moderately stained cells of the convoluted tubules.
Figs. 28&29: kidney cortex of irradiated group showing faintly stained PAS +ve materials in the glomeruli and some epithelial cells of the convoluted tubules after 7 and 30 days respectively.
Figs. 30&31: kidney cortex of OLE group showing almost moderately stained PAS +ve materials after 7 and 30 days respectively.
Figs. 32&33: kidney cortex of R+OLE group showing intensely stained PAS +ve materials in kidney cortex tissues after 7 and 30 days respectively.
Fig. 34: kidney cortex of R+MSCs group showing almost moderately stained of PAS +ve materials after 30 days.

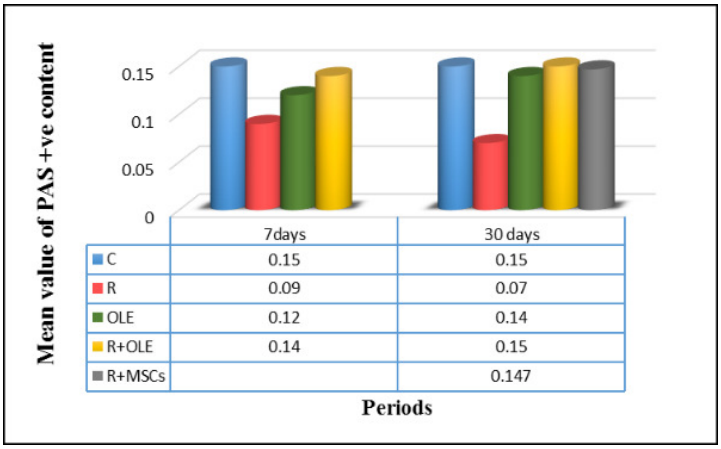
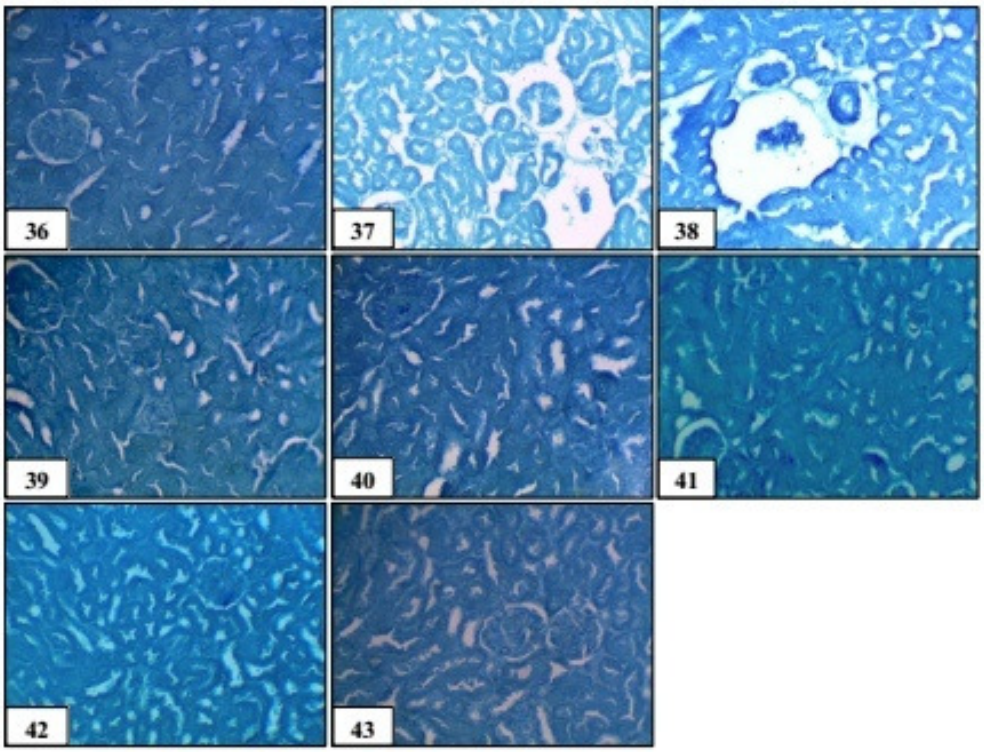


Fig. 35: effect of olive leaves extract or mesenchymal stem cells (MSCs) on the PAS +ve materials in kidney cortex of γ-irradiated adult male rats.



Figs. 36-43: photomicrographs showing distribution of total protein in kidney cortex of the control and treated groups after 7 and 30 days of irradiation (Bromophenol blue X 100).

Fig. 36: kidney cortex of a control rat showing normal distribution of total protein in glomerular capillaries and convoluted tubules.

Figs. 37&38: kidney cortex of irradiated group showing weak stain affinity in the lobulated glomeruli, but some epithelial cells of the convoluted tubules and hemorrhagic area acquired densely stain affinity after 7 and 30 days of γ- irradiation respectively.

Figs. 39&40: kidney cortex of OLE group showing more or less normal distribution of total protein in the glomeruli and convoluted tubules after 7 and 30 days of treatment respectively.

Figs. 41&42: kidney cortex of R+OLE group showing almost normal total protein content after 7 and 30 days of γ- irradiation respectively.

Fig. 43: kidney cortex of R+MSCs group showing nearly normal total protein content after 30 days of γ-irradiation.

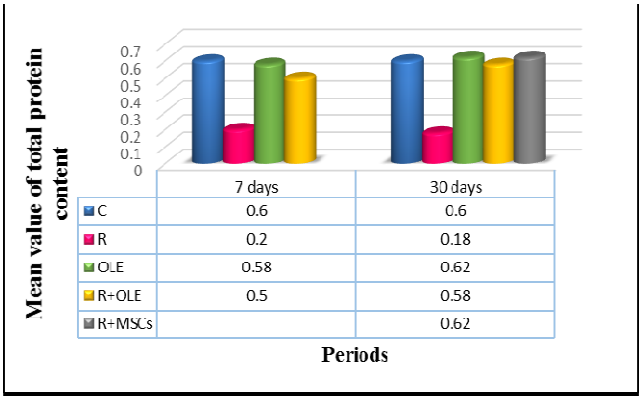
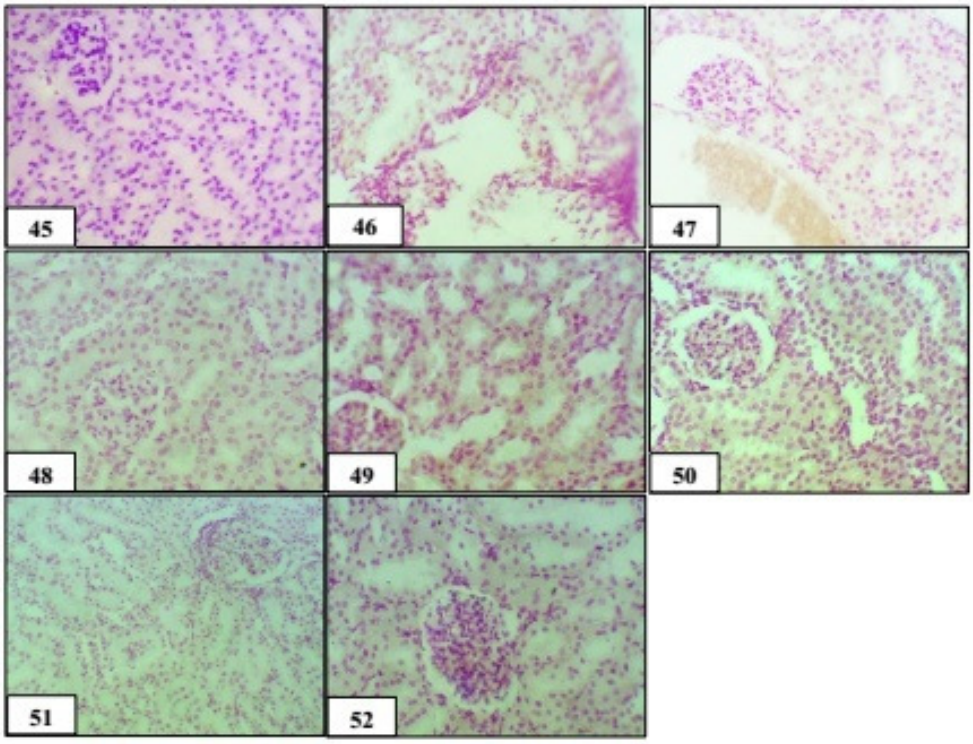


Fig. 44: effect of olive leaves extract or mesenchymal stem cells (MSCs) on the total protein content in kidney cortex of γ-irradiated adult male rats.



Figs. 45-52: photomicrographs showing distribution of total DNA content in kidney cortex of the control and treated groups (Feulgen stain X 200).

Fig. 45: kidney cortex of a control rat showing normal distribution of DNA in glomerular capillaries and convoluted tubules.

Figs. 46&47: kidney cortex of irradiated group showing decreased total DNA content with faint stain affinity in the glomeruli and in the epithelial cells of proximal and distal convoluted tubules after 7 and 30 days post-irradiation respectively.

Figs. 48&49: kidney cortex of OLE group showing more or less normal distribution and moderately stained total DNA in the glomeruli and convoluted tubules after 7 and 30 days of treatment respectively.

Figs. 50&51: kidney cortex of R+OLE group showing almost normal distribution of total DNA content after 7 and 30 days of γ- irradiation respectively.

Fig. 52: kidney cortex of R+MSCs group showing almost normal distribution of total DNA content after 30 days of γ- irradiation.

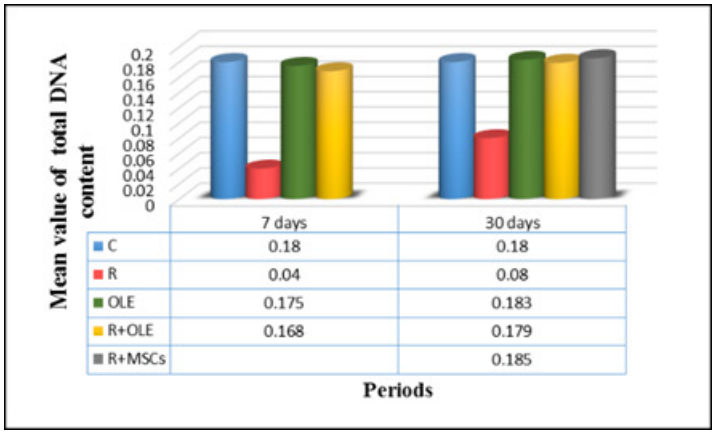
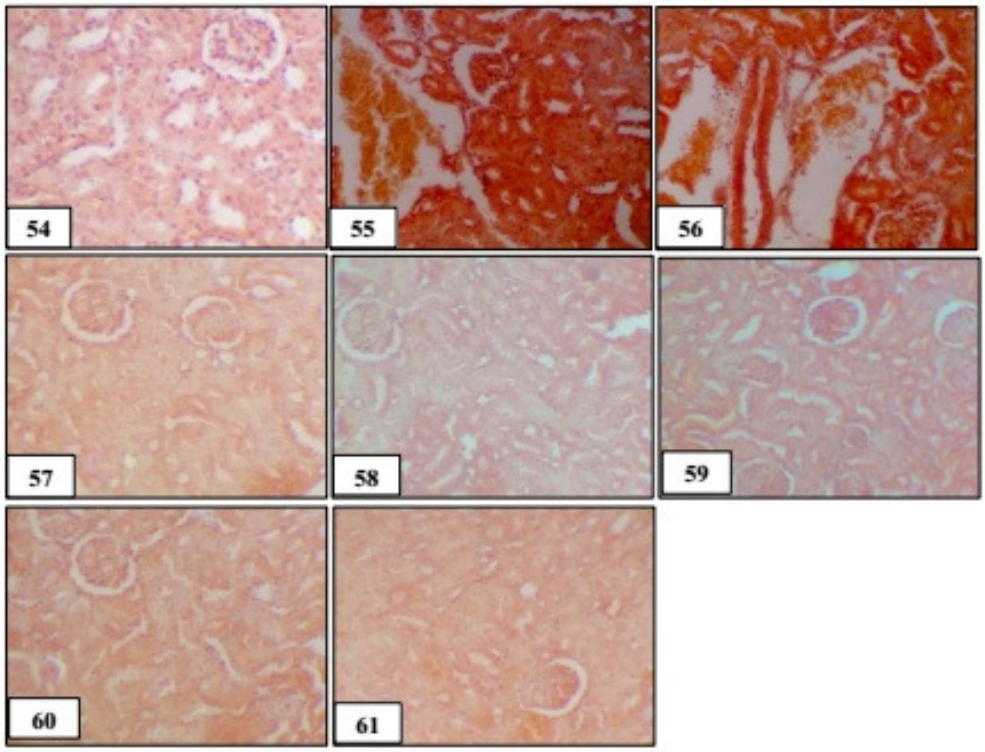


Fig. 53: effect of olive leaves extract or mesenchymal stem cells (MSCs) on DNA content in kidney cortex of γ-irradiated adult male rats.



Figs. 54-61: photomicrographs showing appearance of the amyloid β-protein in kidney cortex of the control and treated groups (Congo red stain X 100).
Fig. 54: kidney tissue of a control rat showing faintly stained amyloid β- protein**.**
Figs. 55&56: kidney cortex of irradiated group showing densely stained amyloid β –protein in the glomerular capillaries, especially in the basement membrane of some convoluted tubules and in hemorrhagic area after 7 and 30 days of gamma irradiation respectively.
Figs. 57&58: kidney cortex of OLE group showing faintly stained amyloid β – protein after 7 and 30 days of treatment respectively.
Figs. 59&60: kidney cortex of R+OLE group showing almost faintly stained amyloid β – proteins after 7 and 30 days of γ- irradiation respectively.
Fig. 61: kidney cortex of R+MSCs group showing almost faintly stained amyloid β-proteins after 30 days of γ-irradiation.

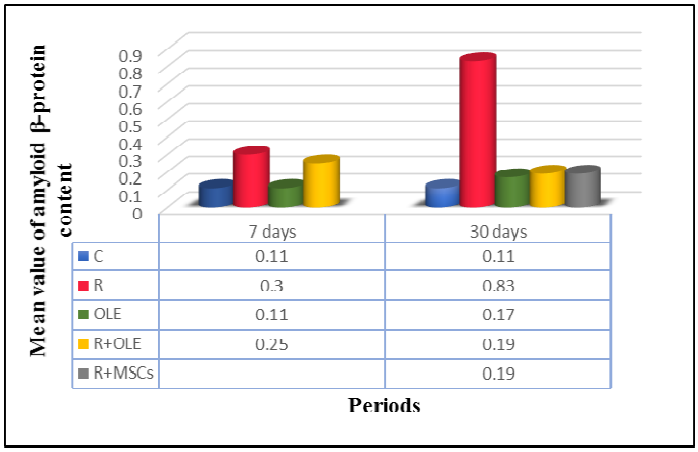


Fig. 62: effect of olive leaves extract or mesenchymal stem cells (MSCs) on the amyloid β- protein content in kidney cortex of γ-irradiated adult male rats.

4. Discussion

Kidney is one of the organs that shows high sensitivity toward gamma-radiation **(Traver *et al*., 2004).** Whole body gamma-irradiation of animals at the sub lethal and lethal dose levels alters the metabolism of various organs and causes a series of biochemical and physiological disturbances in the different biological tissues **(Mohammed, 2010)**.

Hematological studies

Effects of γ-irradiation on renal functions

The present study revealed that exposure of rats to gamma radiation (3Gy) induced a significant increase in renal parameters (serum urea and creatinine) at different intervals of the experiment in comparison with the control group.

Similar findings revealed that whole body gamma irradiation of rats induced a high significant elevation in urea, creatinine and uric acid compared to the control group **(Abd El-Rahman, 2013; El-Desouky *et al*., 2014; Kandil *et al.,* 2015).**

In the present study, a non-significant change in the activities of urea and creatinine were recorded in OLE group during the experimental periods. On the other hand, the irradiated group treated with OLE showed a significant increase in the level of urea and creatinine after 7 days post irradiation. While a non-significant change in the level of urea and creatinine after 30 days of irradiation was observed.

Our results were supported by the findings of **Al-Jubury (2013)**who noticed that treatment with olive leaves extracts showed an improvement in renal parameters (urea, uric acid and creatinine**).** In addition, **Al-Attar *et al.* (2017)** showed that the administration of olive and juniper leaves extracts and their combination in mice can prevent severe alterations of renal hematobiochemical markers and disruptions of its histological structure.

A non-significant change in the concentration of urea and creatinine were recorded in irradiated group injected with MSCs after 30 days of treatment. These results are in agreement with previous studies reported that administration of mesenchymal stem cells (MSCs) improved renal function in rodent models of chronic kidney disease (CKD) **(Quimby *et al.*, 2013)**. In addition, viable bone marrow cells contain sufficient amounts of enzymatic and non-enzymatic antioxidants including SOD, catalase, glutathione peroxidase and glutathione and probably vitamins C and E. The administration of substantial amounts of these viable cells might reinforce the antioxidant capacity of cells and tissues by activating antioxidant recycling mechanism of the renal cells which can restore the balance between oxidant process and the antioxidant defense resulting in a curative effect **(Shindo *et al*., 1994).**

Treating animals with MSCs after being injected with anti-Thy1, 1 revealed an improvement in the histological and histochemical changes. While, apoptosis and the levels of urea and creatinine were decreased **(Sakr *et al.*, 2013)**. Result of the present research work were also in agreement with those described by **Zahkouk *et al.* (2015)** who showed that the levels of urea, uric acid and creatinine were elevated after treatment with cisplatin. However, after MSCs transplantation the level of these parameter showed a significant improvement in the kidney functions.

MDA and GSH in kidney tissue

The present findings showed a significant increase in MDA level and a significant decrease in GSH level in kidney tissue of the irradiated rats when compared to the control. These findings are supported by the results of **Karslioglu *et al*. (2004)** who revealed that rats exposed to whole body gamma radiation showed a significant increase of MDA level after 10 days post-irradiation. Furthermore, **Song *et al.* (2006)** reported that mice irradiated at 4.5 Gy gamma rays had a significant increase of MDA levels.

Membrane lipids are easily affected by reactive oxygen species (ROS) produced by ionizing radiation, causing structural and functional impairment **(Pandey and Mishra, 2003)**. In addition, lipid peroxidation of biological membranes contributes significantly to the development of radiation induced cell injury, because these cellular elements play a decisive role in the functional organization of the cell **(El Tahawy *et al.,* 2008).**

The present findings are also supported by the research of **El-Kabany and Lotfi (2012) and Mansour (2013)** who illustrated that exposure to gamma-radiation resulted in significant decrease in GSH content and significant increase in MDA.

The reduction in GSH content might be due to the inhibition of GSH synthesis or due to the lack of amino acids required for GSH formation **(Sener *et al.,* 2006).** On the other hand, the decrease in tissue GSH levels after irradiation might be due to its consumption during the oxidative stress induced by ionizing radiation **(Kregel and Zhang, 2007; Mansour, 2013). Mansour *et al.* (2014)** reported that ionizing radiation (6Gy) caused a significant increase in liver and kidney malondialdehyde (MDA) level and significant decrease in superoxide dismutase (SOD), catalase (CAT) activities and glutathione (GSH) content. Meanwhile, **Lakshmi *et al.* (2013) and Hussein *et al.* (2016)** suggested that exposure to oxidative stress significantly increased malondialdehyde levels and significantly decreased in superoxide dismutase and catalase activities in the liver and kidneys of rats**.**

Results of the current research revealed that orally drenching OLE induce a non-significant increase in MDA and GSH level after 7 and 30 days of irradiation in comparison with the control. MDA in irradiated rats treated with OLE showed a significant increase after 7 days of irradiation and a non-significant increase after 30 days in comparison with the control group. While, GSH in irradiated rats treated with OLE showed a significant decrease after 7 days of irradiation and a non- significant decrease after 30 days in comparison with the control group. These results illustrated that treatment of the irradiated group with OLE caused an improvement in the MDA and GSH levels.

Ashour (2011) demonstrated that olive leaves extract played as a radioprotectors in reducing the MDA levels in γ-irradiated rats (4, 6 Gy) as a result of reducing the lipid peroxidation due to γ-irradiation.

OLE component namely oleuropein and oleanolic acid, inhibit ROS production thus maintain biological membrane integrity and prevent lipid peroxidation (**Machowetz *et al*., 2007; Castellano *et al.,* 2013**).

Results of the current research work illustrated that irradiated rats injected with MSCs showed a non-significant decrease in MDA and a non-significant increase in GSH level after 30 days of treatment in comparison with the control.

Treatment with MSCs also resulted in a significant reduction in the levels of malondialdehyde (MDA), which is associated with renal injury **(Zhuo *et al.,* 2011)**.

Administration of MSCs induced an increase in the activities of antioxidant enzymes including superoxide dismutase (SOD) and the decreases in malondialdehyde (MDA) levels in lung tissues bleomycin-induced pulmonary fibrosis **(Ni *et al.,* 2015)**.

The histopathological and histochemical changes in kidney tissue

The histopathological changes

The kidney is a major potential route for the absorption of hazardous materials encountered in the environment **(Gholampour *et al*., 2011).**

The present, histopathological examination of kidney tissue of the irradiated rats after 7 days showed many deleterious changes in kidney cortex of the exposed group. These changes included: congested, lobulated and atrophied glomeruli, most tubules lost their normal architecture**,** numerous intertubular hemorrhagic areas, cellular debris**,** pyknotic nuclei, cellular detachment, intertubular leukocytic in filtration, edema between renal tubules and thickening of atrial wall**.** Some of the convoluted tubules showed hydropic degeneration and cloudy swelling with faint staining affinity, poorly detected brush borders of the proximal convoluted tubules, similary, after 30 days of irradiation sever changes were observed, atrophied, congested and lobulated glomeruli with wide empty spaces, wide Bowman's spaces, intertubular hemorrhagic areas, edema between renal tubules, thickening of atrial wall and prominent signsof degeneration in some epithelial cells of the distal convoluted tubules**.**

The detection of destructed cells lining the proximal and distal tubules in the present study was similar to that observed by **Jaenke *et al.* (1993) and Abu-Nour (2002)**. They concluded that the tubular cells were among the most important target cells for radiation injury and the endothelial cell injury represented the primary site of radiation damage in kidney.

Abdel-Gawad *et al.* (2000) noticed that the effect of whole body gamma irradiation in female rats showed changes that varied from mild tubular degeneration to renal necrosis. Irradiation of kidney has been reported to cause progressive injury that results in fibrosis, renal failure and glomerular injury. Similar results were obtained by **Agostino *et al.* (2001) Kandil *et al*. (2015) and Cohen *et al*. (2015).** who stated that the whole irradiated animals had severe renal damage involving glomeruli, tubules, interstitial tissue and blood vessels.

In the current study kidney tissue of animals drenched olive leave extract (OLE) alone showed more or less normal appearance of Bowman's capsules and the convoluted tubules after 7and 30 days. While, animals exposed to radiation after drenching olive leaf extract showed almost normal appearance, but some renal tubule with pyknotic nuclei and few debris in their lumen were still noticed.

The effective role of the extracts may partially have been explained by hypotensive effects of olive leaf extract that make kidney work normally **(Nekooeian *et al.,* 2011).** OLE showed less inflammatory reaction in the renal tissues that might be attributed to OLE's anti-inflammatory effects **(Chebbi *et al.,* 2011).** Meanwhile, **Morgana *et al.* (2014)** demonstrated that kidney of rats treated with olive after exposure to oxidative stress showed normal renal glomeruli and tubules with slight congestion. Further, studies showed diabetic adult male albino rats treated with aqueous OLE only, revealed relative improvement of histological changes (**Mehanna *et al.*, 2016).**

In the present investigation, injection of irradiated rats with MSCs revealed almost normal appearance of kidney cortex, but some renal tubule with pyknotic nuclei and few debris in their lumen were still noticed after 30 days of irradiation. MSCs have the capacity to repair renal injury, accelerate tubular proliferation, improve renal function,

upregulate HO-1 expression and increase HO activity, all are essential for MSC growth and differentiation to the osteoblast lineage, which is consistent with the role of HO-1 in hematopoietic stem cell differentiation (**Vanella *et al*., 2012**).

Bahlmann and Fliser (2009) illustrated that injection with MSCs can accelerate functional repair of injured nephrons, most likely through paracrine mechanisms. MSCs also played a special role in inhibiting inflammatory reactions and promoting tissue repair **(Hanson *et al.,* 2010; Tu *et al.*, 2012). Yagi *et al.* (2010)** demonstrated that transplantation of bone marrow mesenchymal stromal cells can attenuate the effects of systemic inflammation and organ injury in two different animal models of injury. This therapeutic effect was observed in all three vital organs (liver, kidney and lung) in animals demonstrating the anti-inflammatory and anti-apoptotic effects of MSCs.

Treating animals with MSCs revealed that kidney tissue displayed an improvement in the histological and histochemical changes. The inflammatory cells were reduced and hypertrophoid glomeruli were absent **(Sakr *et al.,* 2013 and Zahkouk *et al.,* 2015)**.

Both olive leaf extract and stem cell therapy have radio protective effect as they reduced the pathological cellular injuries in the liver cells induced by accumulated doses of radiation (6Gy as fractionated dose) exposure **(Abu-Amara and Meselhy, 2016)**.

The present study showed highly increased collagen fibers in the tissue of kidney cortex of irradiated group especially in the brush borders and basement membranes of the convoluted tubules. Hemorrhagic areas were also realized. **George *et al.* (2001)** suggested that decreased synthesis of collagenolytic enzymes by the impaired hepatocytes might contribute to further accumulation of collagen.

In the irradiated rat (6 Gy), the amount of collagenous fibers in both cortex and medulla were obviously increased around the damaged basement membranes of the renal tubules. Clear interstitial hemorrhage in the shrunken glomerular tufts was detected around the damaged renal tubules of the cortical region and Bowman's capsule **(Abd El-Azeem, 2011).** Moreover, **El- Dahshan (2013)** detected an increased collagen fibers in kidney cortex of newly born mice of the irradiated group.

Mallory trichrome stain demonstrated almost normal distribution of collagen fibers in the Bowman's capsules, brush borders of the proximal convoluted tubules, glomeruli and the basement membranes of the convoluted tubules in kidney tissue of OLE, R+ OLE and R + MSCs groups during the two experimental periods. kidney architecture could be attributed to the presence of oleuropein which is the most prominent phenolic compound in the olive leaves extract that has anti-inflammatory and antioxidant properties **(Visioli *et al.,* 2002)**.

In addition, **Mousa (2016)** showed that diabetic rats treated with olive leaves extract at the same dose exhibited highly reduced fibrosis inside the seminiferous tubules and almost normal distribution of collagen fibers similar to the control group.

After treatment of irradiated rats with OLE and/ or MSCs the amount of collagenous fibres deposition was significantly decreased around hepatic sinusoids, central vein and portal tract structures in comparison with their radiated group (**Abu-Amara and Meselhy, 2016)**.

The histochemical changes

Polysaccharides

The present study revealed a significant decreased of polysaccharides in proximal and distal convoluted tubules in renal tissue of the irradiated group, but they were increased especially in congested glomeruli, the brush borders and the basement membrane of the convoluted tubules. These changes in polysaccharides may be due to failure of Golgi apparatus to synthesize carbohydrate or due to lytic enzymes released from ruptured lysosomes or due to hypoxia **(Zaghloul and Salem, 2001; Koyu *et al*., 2005)**

Reduced stain affinity of PAS +ve materials was detected in kidney tissue in irradiated rats at dose 2Gy **(Emam *et al.,* 2013)**. The reduction of PAS +ve materials was also noticed by **Eid *et al.* (2015)** who observed a significant decrease of PAS +ve materials in the central and portal areas in liver of adult male albino rats exposed to RF-EMF from mobile phone radiation 900 MHz. Exposure of rats to 4 Gy of gamma radiation showed a significant decrease in the PAS +ve materials in the testis of rat after 5 days or 21 days of γ- irradiation **(Eid *et al.,* 2016)**.

The present study showed a non-significant change in the mean value of PAS +ve materials in kidney tissue of OLE, R+OLE and R+MSCs groups after 7 and 30 days of γ- irradiation. Similar results were obtained by **Tavafi *et al.* (2012)** who found that OLE is a new nephroprotective agent against acute kidney failure. In addition, administration of oil leaf extract or bone marrow mesenchymal stem cells (BMSCs) provides good therapeutic effect against gamma radiation induced histological and histochemical alterations in lungs of male albino rats. A better ameliorative effect was obvious in BMSCs treatment **(Abd El-Hady and AlJalaud, 2015)**.

Such restoration may also be due to the increase in the activities of antioxidant enzymes including superoxide dismutase (SOD) and the decreases in malondialdhyde (MDA) levels in lung tissues **(Ni *et al.,* 2015).** In both OLE and MSCs irradiated treated

groups most of the hepatocytes revealed significant improvement of PAS+ve reaction **(Abu-Amara and Meselhy, 2016).**

Total protein

In the present findings, exposure of rats to gamma radiation (R) represented a significant decrease in the mean value of total protein in kidney tissue after 7 and 30 days of γ- irradiation.

Similar findings were obtained by **Badr El-din (2004)** who stated that a single dose of total body gamma irradiation (6.5 Gy) to mice induced detectable decrease in total protein. This reduction in protein content may be due to the decreased ability of tissue to produce proteins **(Al Gahtani, 2006).**

Decreased total protein in the glomeruli, Malpighian's corpuscles, walls of the convoluted tubules with negatively stained degenerated areas were noticed in kidney cortex of irradiated (2Gy) pregnant rats **(Bakhit, 2013)**.

The present results are in contrast with increased total protein in various tissue post exposure to different types of radiations noticed by many authors **(Abu El Naga, 2012; Emam *et al.,* 2013).** Also, **Ni *et al*. (2015) and Abd El-Hady and Al-Jalaud (2015)** showed that increased total protein content of lung tissue post exposure to oxidative stress, highly affected protein and DNA post-irradiation exposure this may be due to the response of hydrogen bonds of these materials to radiation **(Bakhit, 2010).**

In the present study rats which were administrated olive leaves extract **(OLE)** alone or after exposed to γ- radiation showed a non-significant change in the mean value of total protein compared to the control group in kidney tissue. The improvement in protein content in OLE and R+OLE may be due to oleuropein which stimulated endothelium formation as well as synthesis of mRNA and protein **(Carluccio *et al.*, 2003)**. It may also be due to the increase amount of ribosomes in rough endoplasmic reticulum in cells, reflecting their ability to stimulate protein synthesis **(Tunez *et al.,* 2003).**

Results obtained showed that injection of rats with mesenchymal stem cells (MSCs) post exposed to radiation showed a non-significant increase in the mean value of total protein after 30 days of γ-irradiation in the glomerulus and renal tubules of kidney tissue.

Treatment with bone marrow post-irradiation exposure showed normal appearance of total protein content of the liver and lung tissues of pregnant rats exposed to 2Gy of γ-rays (**Bakhit, 2010).** Furthermore **Emam *et al.* (2013)** demonstrated that bone marrow transplantation after exposed to 2Gy of gamma radiation showed more or less normal appearance of the total proteins in the maternal cardiac tissue in comparison with the control. **Abd El-Hady and Al-Jalaud (2015)** observed that almost normal total protein content was reported earlier in the fetal lung tissue maternally treated with the bone marrow cells post-irradiation.

DNA content

Exposure of rats to 3 Gy of gamma radiation **(R)** illustrated a significant decrease in the mean value of DNA material represented by faint stain affinity in both proximal and distal convoluted tubules in kidney tissue, but cellular infiltration area acquired densely stained affinity throughout the two experimental periods. Ionizing radiation exerts its effects mostly on the cells' genomic information, either by directly depositing its energy onto DNA molecules or by creating free radicals that in turn interact with the DNA strands **(Mahaney *et al.,* 2009).**

Similar findings were obtained by **Purohit *et al.* (2007)** who noticed that in irradiated animals, the values of glycogen and DNA decreased in kidney tissue continuously up to day-7 and increased thereafter up to day-28. Further study illustrated that the decrease of DNA content was associated with a decrease in protein content in kidney cells of the rats exposed to free radicals **(Eid *et al.,* 2014).**

El-Shawi and Abd- El Rahman (2016) showed that radiation exposure resulted in increased percentage of DNA damage and DNA fragmentation.

The present study showed a non-significant change in total DNA content in kidney cortex in the groups treated with OLE, R + OLE and R+MSCs in comparison with the control. This improvement in OLE and R + OLE could be due to the antioxidant properties of olive oil-derived phenolic compounds (oleuropein and hydroxytyrosol) which are linked with inhibition of lipid peroxidation and free radical scavenging activity **(Tuck *et al.,* 2001)**. In addition to quenching ROS directly, oleuropein was reported to effectively prevent protein, lipid or DNA from oxidative damage by regulating other cellular antioxidant systems **(Fatani *et al.,* 2015)**. Also, olive leaf polyphenols are anti-inflammatory and protect against DNA damage initiated by free radicals **(Boss *et al.,* 2016)**.

Stem cells can be transplanted to replace non-functional or lost stem cells in tissues to accelerate tissue healing and restore the original function **(Burt *et al*., 2008).** The regenerative potential of stem cells was studied by **(Kirsch *et al.,* 2010; Makridakis *et al*., 2013).** Due to their radio resistant phenotype, MSCs may qualify as a therapeutic means to treat radiation-induced DNA damage via different recognition pathways and other radiation-induced tissue damage **(Nicolay *et al.,* 2015)**.

Amyloid- β protein

The current study recorded a significant increase in the amyloid-β protein content in kidney tissue in

glomerular capillaries, especially in the basement membrane of some convoluted tubules and in hemorrhagic areas in kidney tissue of the irradiated animals throughout the experimental periods.

Oxidative damage is associated with Alzheimer's disease and mild cognitive impairment, but its relationship to the development of neuropathological lesions involving accumulation of amyloid-beta peptides and hyper-phosphorylated protein **(Goldsbury *et al.*, 2008).** Meanwhile, **Eid *et al.* (2016)** showed that exposure of rats to gamma radiation increased amyloid β-proteins in the testicular tissues especially in the thickened wall of the congested testicular artery and the hemolysed blood cells after 5 or 21 days of γ- radiation exposure.

The present finding showed a weak stain affinity and a non-significant increase in the mean value of amyloid β- protein (Aβ) content in OLE and R+OLE groups after 7 and 30 days of treatment in kidney tissue.

Antioxidant treatments in the early stages of pathogenesis were able to alleviate the functional impairment **(Hsiao *et al.*, 2012)** and to reduce brain Aβ in AD mouse models **(Chu, 2012; Cheng *et al.*, 2014).**

Qosaa *et al.* (2015) showed that feeding mice with extra-virgin olive oil (EVOO)-enriched diet for 3 months, beginning at an age after Aβ accumulation starts, showed improved clearance across the blood brain barrier and significant reduction in Aβ levels.

In the present study irradiated rats injected with MSCs post exposed to γ- radiation exhibited faintly stained amyloid-β protein and represented a non-significant increase in the mean value of amyloid β-protein content after 30 days of γ- irradiation in kidney tissue compared to the control rats**.**

Intracerebral transplantation of BM-MSCs into the brain of an induced AD model reduced their Aβ levels when compared to the control animal **(Trzaska *et al.*, 2008).** These findings also agree with **Lee *et al.* (2009)** who stated that transplanted BM-MSCs caused reduction in Aβ in induced AD mice. Similarly, **Gabriela *et al.* (2015) and Turgeman (2015)** showed that bone marrow derived MSCs injected intracerebral were effective in reducing accumulation of amyloid-β (Aβ) in the brain of an animal model of AD.

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