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The potential protective role of taurine against 5-fluorouracil-induced nephrotoxicity in adult male rats

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ABSTRACT

Nephrotoxicity is common with the use of the chemotherapeutic agent 5-Fluorouracil (5-FU). The current study aimed to investigate the probable protective effect of taurine (TAU) against 5-FU-induced nephrotoxicity in rats using biochemical, histological and ultrastructural approaches. Twenty-four rats were equally divided into control, TAU, 5-FU and 5-FU + TAU groups.

5-FU significantly elevated levels of blood urea nitrogen (BUN), creatinine, and uric acid; while it reduced activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). Also, 5-FU induced significant elevation in malondialdehyde (MDA) levels accompanied with marked decline in γ-glutamyltranspeptidase (GGT) and alkaline phosphatase (AP) levels in kidney tissues. These biochemical alterations were accompanied by histopathological changes marked by destruction of the normal renal structure, in addition to ultrastructural alterations represented by thickened and irregular glomerular basement membranes, congested glomerular capillaries, damaged lining fenestrated endothelium, mesangial cells hyperplasia with expanded mesangial matrix, and distorted podocyte's processes. Also, the proximal (PCT) and distal (DCT) convoluted tubules showed thickened basement membranes, destructed apical microvilli and loss of basal infoldings of their epithelial cells.

Administration of TAU to 5-FU-treated rats reversed most of the biochemical, histological, and ultrastructural alterations. These results indicate that TAU has a protective effect against 5-FU-induced nephrotoxicity.

1. Introduction

5-Fluorouracil (5-FU) is one of the most commonly used chemotherapeutic drugs in the treatment of various types of human malignancies, like breast, head, neck, stomach, gastrointestinal, liver and skin cancers (Sausville and Longo, 2001; Xiao et al., 2001; Yoshikawa et al., 2001; Liu et al., 2002; Miura et al., 2010; Kocar et al., 2016).

5-FU is a pyrimidine analog and it is converted intracellularly to active metabolites, including fluorodeoxyuridine monophosphate, fluorodeoxyuridine triphosphate, and fluorouridine triphosphate. 5-FU exerts its anticancer effects by integrating its toxic metabolites into RNA and DNA and inhibiting the nucleotide synthetic enzyme thymidylate synthase (Chibber et al., 2011; David et al., 2011).

Like other chemotherapeutic drugs, 5-FU is non-targeted in action and results in RNA and DNA damage and cell death leading to extensive side effects like myelotoxicity, leukopenia, gastrointestinal toxicity, diarrhoea, vomiting, mucositis, alopecia and cardiotoxicity (Kinhult et al., 2003; Tsibiribi et al., 2006; David et al., 2011; Chang et al., 2012; Lamberti et al., 2012). Besides, it was reported that 5-FU is catabolised into dihydrouracil in the liver which is cleaved into a-fluoro-b-alanine, urea, ammonia, and carbon dioxide, thereby leading to hepatotoxicity and nephrotoxicity (Ali, 2012; Rashid et al., 2014).

Taurine (TAU; 2-aminoethanesulfonic acid) is one of the most abundant free amino acids in animal cells and tissues. It is found in high concentrations in the liver, brain, heart and kidneys of mammals. It is synthesized in the liver from cysteine and methionine and ingested directly in certain foodstuffs as meats, seafood, and milk (Huxtable, 1992). Several studies demonstrate that TAU has antioxidant, anti-inflammatory, antitumorigenic and hepatorenal protective potential (Tabassum et al., 2007; Kim et al., 2013; Marcinkiewicz and Kontny, 2014).

In literature, there are few studies related to the effect of TAU on the biochemical, histological and ultrastructural alterations that may occur in kidney tissues of mammals as a result of 5-FU exposure. Therefore, the current study was conducted to

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investigate the probable protective influence of TAU against the toxic effects induced in the kidney tissues of adult male albino rats as a consequence of 5-FU administration.

2. Materials and methods

2.1. Pharmacological materials

5-FU is manufactured by EBEWE Pharma Ges.m.b.H. Nfg. KG. A-4866 Unterach, AUSTRIA. It is available in packages enclosing five ampoules, each containing 250 mg/5 ml of 5-FU. TAU was purchased from Sigma Chemical Co. (St Louis, MO, USA). All other chemicals used in the present study were of analytical grade of Merck quality.

2.2. Experimental animals

Twenty-four adult male albino rats (*Rattus norvegicus*) of similar age (3–4 months) and weight (160- 180 g) were obtained from the animal house of Theodor Bilharz Research Institute (TBRI), El-Giza, Egypt. They were housed in clear plastic cages (2 animals/cage) with wood chips as bedding in a room with a temperature range of 25 ± 2 °C, relative humidity of 55 ± 5% and a 12-h light/dark cycle. Standard laboratory rodent chow and tap water were provided ad-libitum. The animals were acclimatized for a period of one week prior to the commencement of the experiment. All animal experiments were performed under protocols approved by the local Institutional Animal Ethics Committee of Ain Shams University.

2.3. Experimental design

The rats were divided randomly into four groups of six animals each as follows:

Group I (Control group): Rats were given the normal saline parallel to the treated groups throughout the course of the study.

Group II (TAU group): Rats were orally received TAU (50 mg/kg bw/day) dissolved in distilled water (1 ml per animal) by gastric tube for 7 days. This dose was based on previously published studies which showed that this dose was effective against the toxicity induced by various xenobiotics (Çetiner et al., 2005; Sener et al., 2005a,b,c).

Group III (5-FU group): Rats were intraperitoneally (i.p.) injected with 5-FU (20 mg/kg bw/day) for 7 days. This dose was chosen according to the work accomplished by Takizawa and Horii (2002), El-Sayyad et al. (2009) and Ali (2012).

Group IV (5-FU + TAU group): Rats were orally administered TAU (50 mg/kg bw/day) alone for 7 days pre-treatment with 5-FU, subsequently they were administered TAU for another 7 days parallel with i.p. injection with 5-FU (20 mg/kg bw/day), after that they were orally given TAU (50 mg/kg bw/day) alone for another 7 days (post treatment with 5-FU).

2.4. Collection of blood and tissue samples

At the end of the experimental time period, control and treated animals were fasted overnight and then anesthetized under light ether anesthesia. Blood samples were collected by cardiac puncture then centrifuged at 1500*g* for 10 min at 4 °C to obtain sera which were immediately stored at −80 °C until use. Kidneys of rats were dissected out and washed immediately with ice-cold physiological saline (0.9% NaCl). Samples from the kidneys were stored frozen at −80 °C for further biochemical analyses, whereas other kidney samples were used for histological and ultrastructural studies.

2.5. Preparation of tissue homogenates

Tissue homogenates were prepared from kidney samples by homogenizing the tissue in ice-cold 0.9% NaCl to obtain a 10% solution using Ultra Turrax tissue homogenizer. Samples were immediately centrifuged (10,000*g* for 15 min) at 4 °C to remove debris, and the clear supernatant fluids were separated and used for the biochemical estimations.

2.6. Biochemical assessment

2.6.1. Renal functions assessment

Specific markers related to renal function including levels of blood urea nitrogen (BUN), creatinine and uric acid in the sera were estimated spectrophotometrically using commercial diagnostic kits (Sigma Diagnostics (I) Pvt. Ltd, Baroda, India).

2.6.2. Assay of tissue biomarkers

Lipid peroxidation in tissue homogenates was estimated based on the formation of thiobarbituric acid reactive substances (TBARS) and expressed as the extent of malondialdehyde (MDA) production following the method of Buege and Aust (1978).

Superoxide dismutase (SOD) activity was determined as described previously by Sun et al. (1988) and expressed as units/mg protein using standard calibration curve. Catalase (CAT) activity was determined by the method of Greenwald (1985) and expressed as nmol H_2O_2 consumed/min/mg protein. Glutathione peroxidase (GSH-Px) activity was assayed spectrophotometrically following the method of Mohandas et al. (1984) and expressed as μmol/min/mg protein.

Kidney tissue γ-glutamyltranspeptidase (GGT) and alkaline phosphatase (AP) activities were measured by using the method of Tate and Meister (1985) and Tenenhouse et al. (1980), respectively. Protein contents in the kidney homogenates were estimated according to the method of Lowry et al. (1951) using bovine serum albumin as standard.

2.7. Histological preparations

Samples from the kidneys of the control and experimental animals were rapidly fixed in aqueous Bouin's fixative for 24 h. Then, they were subjected to the normal procedures for paraffin sectioning. After routine processing, 4 μm sections were cut, stained with haematoxylin-eosin (H & E), dehydrated in ascending series of ethyl alcohol, cleared in xylene and mounted in DPX (Bancroft and Gamble, 2002). The stained sections were examined with a light microscope and photomicrographs were made as required.

2.8. Ultrastructural preparations

Small pieces of the renal cortices from the control and treated rats were immediately fixed in cold 4F1G (4% formalin + 1% glutaraldehyde adjusted at pH 2.2) for 24 h, then were post fixed in 1% osmium tetroxide in 0.1 M phosphate buffer (pH 7.3). After fixation, they were subjected to the normal procedures for ultrastructural evaluation by transmission electron microscopy as described previously by Dykstra et al. (2002). After routine processing, the stained grids were examined and photographed by JEOL.JEM-1400-EX-ELECTRON MICROSCOPE at the Electron Microscopy Department of TBRI, El-Giza, Egypt.

2.9. Statistical analysis

The biochemical results were expressed as mean ± SEM of 6 rats per group, Statistical differences among groups were calculated using one-way analysis of variance (ANOVA) using the SPSS/17.0 software followed by Duncan's new multiple-range test. A P-value < 0.05 was considered statistically significant.

3. Results

3.1. Biochemical analysis

Kidney function assessed parameters are presented in Table 1. Non-significant changes in all the measured renal function indices were recorded in the TAU-treated group as compared with the control group. Meanwhile, the assessed renal markers elevated markedly ($P < 0.05$) in sera of the 5-FU-treated rats with percentages of change of 78.59%, 34.61% and 50.81% higher than those of control rats for BUN, creatinine, and uric acid, respectively. Administration of TAU for 7 days pre-, co-, and post-treatment with 5-FU markedly ($P < 0.05$) reduced the rise in the levels of the measured renal function parameters.

As shown in Table 2, administration of 5-FU for 7 days significantly ($P < 0.05$) reduced the activities of SOD (−27.46%), CAT (−64.47%) and GSH-Px (−32.96%) compared with those of control animals. Concomitant administration of TAU with 5-FU significantly ($P < 0.05$) lowered the disturbances in the measured oxidative stress parameters that occurred following treatment with 5-FU alone. Administration of TAU alone did not affect the values of these indices compared to the control group.

Table 3 depicts levels of MDA, GGT, and AP in kidney tissues of control and experimental groups of animals. The results revealed non-significant changes in the levels of these indices when the TAU-treated group was compared with the control group. On contrast, 5-FU induced significant elevation ($P < 0.05$) in MDA level (46.43%) accompanied with a significant decline ($P < 0.05$) in levels of GGT (−50.72%) and AP (−41.88%) in kidney tissues as compared to the corresponding control group. Supplementation of TAU to the rats treated with 5-FU resulted in modulation of these parameters compared to the rats subjected to 5-FU alone.

3.2. Histological observations

Light microscopic examination of the renal cortex of control and TAU-treated rats revealed normal histological structure (Fig. 1A & B). The renal corpuscles appeared morphologically normal with double-walled Bowman's capsules surrounding the glomeruli which formed of a tuft of glomerular capillaries. Bowman's capsules formed of visceral and parietal layers of squamous epithelium with a narrow urinary space in-between. The proximal convoluted tubules (PCTs) appeared with narrow lumina lined with low columnar epithelial cells characterized by the presence of luminal brush borders. Whereas, the distal convoluted tubules (DCTs) attained wider lumina lined with cuboidal epithelial cells.

However, examination of the renal cortex of rats treated with 5-FU showed severe histopathological alterations (Fig. 1C & D). Most of the renal corpuscles lost their normal appearance revealing expanded Bowman's capsules surrounding markedly lobulated and hypertrophied glomeruli with mesangial hypercellularity and congested glomerular capillaries (Fig. 1C), whereas other glomeruli appeared atrophied and shrunken with congested capillaries (Fig. 1D). Severe tubular degeneration was observed in the PCTs and DCTs illustrated by obvious signs of pyknosis of the nuclei of some deteriorated lining epithelial cells and exfoliation of the epithelial cells in their lumina which appeared dilated and occluded with cellular debris, besides shedding of the brush borders of the PCTs (Fig. 1C & D). Also, the same figures demonstrated extensive interstitial hemorrhage and marked infiltration of mononuclear inflammatory cells in the peritubular and perivascular areas, besides enlarged and congested blood vessels.

As illustrated in Fig. 1(E), administration of TAU for 7 days pre-, co-, and post-treatment with 5-FU dramatically improved the pathological changes induced by 5-FU in the renal cortices of the treated rats. The renal corpuscles of the examined renal cortices manifested clear signs of recovery as their Bowman's capsules and glomeruli appeared nearly normal. The PCTs and DCTs almost restored the usual organization of their lining epithelial cells except for the presence of little cell debris in their lumina (Fig. 1E).

Table 1
Levels of blood urea nitrogen (BUN), creatinine and uric acids in sera of control and experimental groups of rats.

Parameter	Group			
	Control	TAU	5-FU	5-FU + TAU
BUN (mg/dl)	24.80 ± 0.92^{a}	25.92 ± 0.42^{a}	44.29 ± 0.86^{b}	29.41 ± 0.53^{c}
Creatinine (mg/dl)	0.52 ± 0.03^{a}	$0.54 \pm 0.01^{a,c}$	0.70 ± 0.01^{b}	0.60 ± 0.01^{c}
Uric acid (mg/dl)	2.46 ± 0.10^{a}	2.42 ± 0.05^{a}	3.71 ± 0.07^{b}	3.07 ± 0.05^{c}

Values are expressed as mean ± SE of 6 animals.
Means with different superscripts within the same row differ significantly at 5% ($P < 0.05$) level of significance.

3.3. Ultrastructural observations

Electron microscopic examination of the renal cortices of control (Fig. 2A & B) and TAU-treated (Fig. 2C & D) rats showed normal ultrastructure of renal corpuscles, where normal double-layered Bowman's capsules with narrow urinary spaces surrounding the glomeruli were observed. The outer parietal layer of Bowman's capsule consisted of flat cells resting upon a thin basal lamina, while its inner visceral layer formed of podocytes which possess highly indented nuclei and electron dense cytoplasm. Each podocyte gives rise to primary processes which in turn give numerous secondary foot processes or pedicles resting on the basement membrane of the glomerular capillaries and leaving narrow filtration slits in-between. The glomeruli formed of capillary loops lined with fenestrated endothelial cells with continuous basement membrane of uniform thickness and electron-dense mesangial cells embedded in the mesangial matrix in-between. The glomerular capillary wall comprised the kidney's filtration barrier which consists of three components; the porous endothelium, the glomerular basement membrane, and the podocyte foot processes with the interposed slit diaphragms (Fig. 2B & D).

On the other hand, obvious ultrastructural changes were detected in the renal cortex of 5-FU-treated rats (Fig. 2E & F). The renal corpuscles revealed dilated and congested glomerular capillaries. The glomerular basement membranes showed local thickening, corrugations, and irregularities. The podocytes revealed small, less indented nuclei and electron-lucent cytoplasm. Some primary podocyte processes were broadened increasing the interstitial spaces between the capillary loops. Marked distortion of secondary podocyte processes was also seen; some of them showed fragmentation or fusion and the others were completely lost. The mesangial cells revealed hyperplasia with dense pyknotic nuclei and expanded mesangial matrix between them. Also, the lining fenestrated endothelium appeared severely damaged, and some of them fused with each other.

Regarding TAU & 5-FU-treated group, electron microscopic examination showed well-preserved cell structures in most of the

Table 2
Levels of antioxidants in kidney tissues of control and experimental groups of rats.

Parameter	Group			
	Control	TAU	5-FU	5-FU+ TAU
SOD (unit/mg protein)	160.90 ± 2.06 [a]	165.26 ± 2.63 [a]	116.72 ± 1.58 [b]	140.25 ± 3.02 [c]
CAT (nmol H_2O_2 consumed/min/mg protein)	45.18 ± 0.75 [a]	46.31 ± 0.70 [a]	16.05 ± 0.24 [b]	39.32 ± 0.85 [c]
GSH-Px (μmol/min/mg protein)	155.80 ± 2.14 [a]	155.71 ± 2.39 [a]	104.45 ± 1.87 [b]	141.23 ± 3.39 [c]

Values are expressed as mean ± SE of 6 animals.
Means with different superscripts within the same row differ significantly at 5% ($P < 0.05$) level of significance. SOD (superoxide dismutase), CAT (catalase), GSH-Px (glutathione peroxidase).

Table 3
Levels of malondialdehyde (MDA), γ-glutamyltranspeptidase (GGT) and alkaline phosphatase (AP) in kidney tissues of control and experimental groups of rats.

Parameter	Group			
	Control	TAU	5-FU	5-FU + TAU
MDA (nmol/mg protein)	5.47 ± 0.17 [a]	5.43 ± 0.09 [a]	8.01 ± 0.13 [b]	6.95 ± 0.09 [c]
GGT (mol/ mg protein/h)	45.80 ± 0.72 [a]	45.39 ± 0.74 [a]	22.57 ± 0.44 [b]	36.31 ± 0.61 [c]
AP (mol/ mg protein/h)	15.21 ± 0.23 [a]	15.94 ± 0.24 [a]	8.84 ± 0.17 [b]	11.25 ± 0.27 [c]

Values are expressed as mean ± SE of 6 animals.
Means with different superscripts within the same row differ significantly at 5% ($P < 0.05$) level of significance.

processed kidney samples. As illustrated in Fig. 2(G & H), the glomerular basement membranes acquired a uniform thickness and normal fenestrated endothelium. The podocytes appeared nearly normal with regular renal filtration barrier basement membrane. However, mild alterations were observed in some renal corpuscles including few glomerular capillary loops with mild congestion.

Electron microscopic examination of the renal cortex of control (Fig. 3A & B) and TAU-treated (Fig. 3C & D) rats showed normal ultrastructural features of the lining epithelial cells of the PCTs where they attained normal basal or mid-positioned oval nuclei with evenly distributed chromatin materials. The apical surfaces of the PCT cells illustrated numerous long microvilli projecting within their narrow lumina, whereas their basal portions revealed abundant deep basal infoldings running perpendicular to their thin regular basement membrane. Their cytoplasm appeared containing rough (RER) and smooth (SER) endoplasmic reticula, free ribosomes, few lysosomes, and numerous rounded to elongated mitochondria having transverse cristae and localized at the base of the cells parallel to the long cell axis.

However, the lining epithelial cells of the PCTs of 5-FU-treated rats showed marked destruction of their apical microvilli, thickening of the basement membranes with degenerated or partially loss of their basal infoldings, cytoplasmic degeneration with swollen mitochondria possessed electron-dense matrices and damaged cristae, hypertrophied RER and SER, increased number of lysosomes and many cytoplasmic vacuoles, beside pyknotic nuclei (Fig. 3E & F).

Examination of the lining epithelial cells of PCTs of rats treated with both 5-FU and TAU revealed nearly normal ultrastructural features compared to those of the control group. As illustrated in Fig. 3(G & H), the microvilli, the basement membranes, and the basal infoldings appeared normal. Also, the cytoplasm appeared with normal mitochondria with closely parallel cristae, RER and SER, free ribosomes and few lysosomes, beside their nuclei showed normal appearance.

The lining epithelial cells of the DCTs of control (Fig. 4A) and TAU-treated (Fig. 4B) rats showed normal fine structure, where they are characterized by the presence of basal infoldings that being lesser than those in the epithelial cells of the PCTs and no conspicuous brush borders were seen at the free cell surfaces. The cytoplasm showing poorly developed RER and SER, free ribosomes, lysosomes and elongated mitochondria with transverse cristae which are fewer than those in the PCTs epithelial cells. Also, they attained spherical and basally located nuclei possessing evenly distributed chromatin materials.

Whereas, the epithelial cells of the DCTs of 5-FU-treated rats (Fig. 4C) showed conspicuous cytoplasmic degeneration and vacuolation, small-sized or degenerated mitochondria with electron dense matrices and many lysosomes. Apoptotic nuclear changes with fragmented nuclear envelopes were seen. Thickening of the basement membranes with irregular, destructed or loss of the basal infoldings was also revealed in Fig. 4(C).

Meanwhile, the DCTs cells of the combined TAU and 5-FU-treated rats showed regular basement membranes with many basal infoldings, well-organized mitochondria and intact nuclei with regular chromatin distribution.

4. Discussion

The kidneys are very sensitive to the adverse effects of chemicals and drugs, as they are involved in filtering and concentrating different chemicals and substances that may reach high concentration and become toxic (Loh and Cohen, 2009). In general, Kintzel (2001) mentioned that nephrotoxicity is a contiguous adverse side effect of the anticancer drugs for hematologic and solid malignancy. 5-FU has been extensively used as a chemotherapeutic agent for a lot of human malignancies (Miura et al., 2010; Rashid et al., 2014). Although 5-FU exerts acceptable outcome, it exhibits severe side effects and it is considered as nephrotoxic agent (Inoue et al., 2009).

Cytoprotective substances can be used in therapy to ameliorate majority of the functional renal disorders (Behling et al., 2006). TAU, a non-protein and semi-essential amino acid, is present in the majority of mammalian cells and it has a strong cytoprotective potential in various statements (Tabassum et al., 2007; Akay et al., 2013; Kim et al., 2013; Marcinkiewicz and Kontny, 2014). Thereby, the current study was carried out to investigate the renal lesions caused by 5-FU and to evaluate the probable nephroprotective effect of TAU against such adverse influences induced by 5-FU in kidney tissues of adult male albino rats.

In the present study, treatment of rats with 5-FU (20 mg/kg bw) once daily for 7 successive days resulted in renal damage as evidenced from the biochemical, histological and ultrastructural

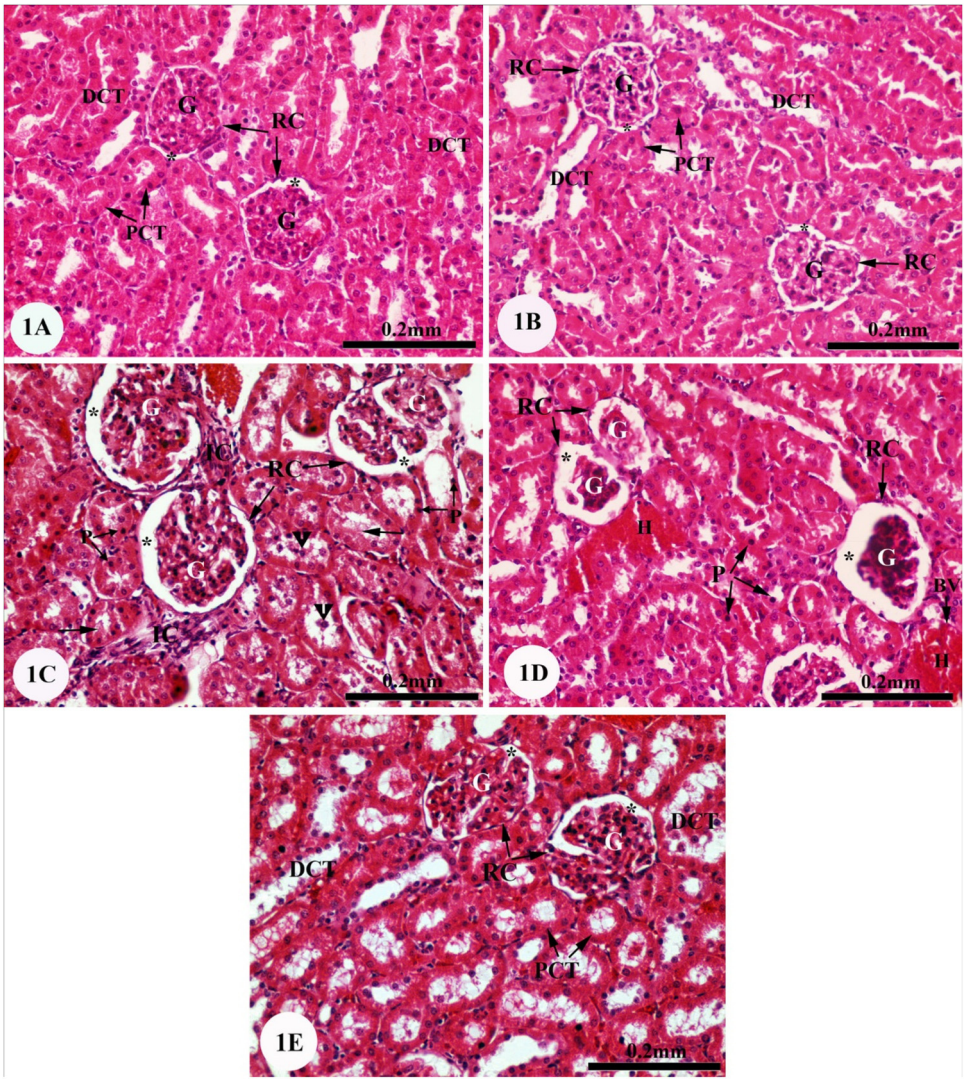

Fig. 1. Light micrographs of the renal cortex of control and treated rats stained with H & E showing (A & B) normal renal corpuscles (RC) consisting of double-walled Bowman's capsules (asterisks) surrounding the glomeruli (G), PCTs and DCTs in control and TAU-treated rats, respectively. (C) Distorted renal corpuscles (RC) revealing markedly dilated Bowman's capsules (asterisks) surrounding lobulated and hypertrophied glomeruli (G) with mesangial hypercellularity are seen in 5-FU-treated rats. Also, deformed PCTs and DCTs exhibiting pyknotic nuclei (P) of some of their lining epithelial cells, exfoliated epithelial cells (black arrowheads) and erosion of the brush borders (black arrows) within their lumina, beside interstitial inflammatory cell infiltration (IC) are noticed. (D) Deteriorated renal corpuscles (RC) with widened Bowman's capsules (asterisks) surrounding atrophied and shrunken glomeruli (G) exhausting glomerulosclerosis, pyknotic nuclei (P) of epithelia of the PCTs and DCTs, dilated blood vessel (BV) engorged with hemorrhagic blood masses (H) are seen in 5-FU-treated rats. (E) Marked improvement of the renal corpuscles (RC) with normal Bowman's capsules (asterisks) and glomeruli (G). Besides, the PCTs and DCTs nearly restored their normal structure in 5-FU & TAU-treated rats.

findings. However, treatment of rats with TAU alone (50 mg/kg bw/day) for 7 successive days did not induce any marked changes in the above-mentioned indices.

Serum BUN, creatinine, and uric acid levels are the most predisposed markers reflecting the appropriate function of the kidney (Gowda et al., 2010). The obtained results from the current study showed impaired kidney function in rats treated with 5-FU relative to the corresponding control ones as evidenced by the elevated levels of the assessed renal function indices. These findings are in agreement with those previously reported (Ali, 2012; Rashid et al., 2014); while co-administration of TAU with 5-FU significantly improved the assessed kidney function parameters. In the same context, the improved renal function by TAU supplementation has been manifested by previous studies (Saad and Al-Rikabi, 2002; Hagar et al., 2006; Islambulchilar et al., 2015).

Antioxidant enzymes, including SOD, CAT and GSH-Px are the first line cellular defense enzymes against oxidative injury by scavenging the generated free radicals. Oxidative stress causes tissue damage when the generated free radicals exceed the cell's capacity for their neutralization via the antioxidant enzymes (Nath and Norby, 2000). Another indicator of oxidative stress in biological systems is the level of MDA, one of the lipid peroxidation products (Wiland and Szechcinski, 2003; Karahan et al., 2005). Data of the present study showed that 5-FU administration was associated with oxidative stress as evidenced by marked elevation of MDA level accompanied with a marked decline in the activities of SOD, CAT, and GSH-Px in the renal tissues. Such changes were similar to the results of Chen et al. (1997) and Rashid et al. (2014). Moreover, our results indicated that the levels of GGT and AP, the prevalent enzymes found in the brush border of the kidney microtubules, were decreased due to 5-FU intoxication which reflects damage of the kidney microtubules. Close result was also reported by other researchers on treating rats with the anticancer drug cisplatin (Fatima et al., 2007; Khan et al., 2009; Ahn et al., 2014).

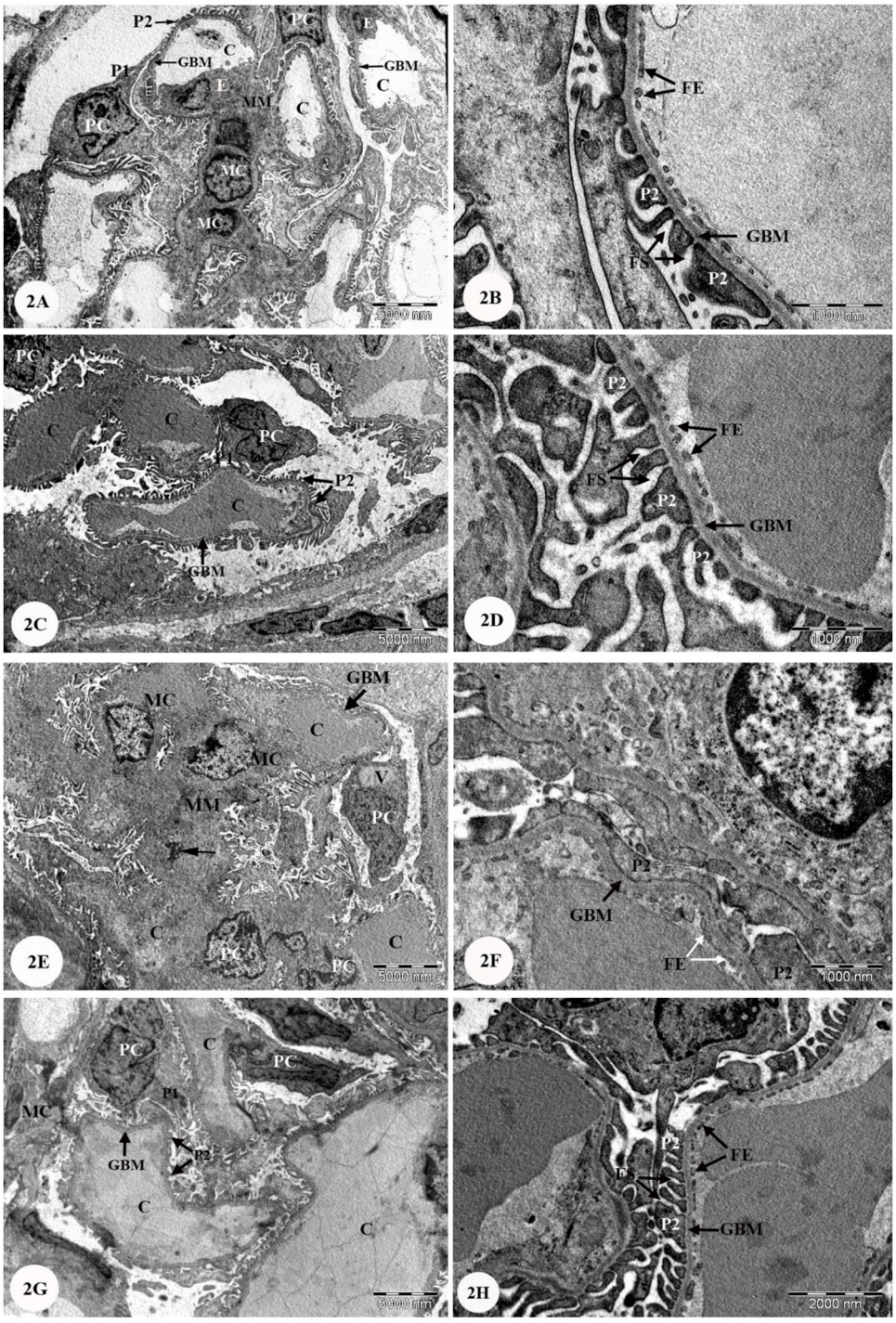

Fig. 2. Electron micrographs of renal corpuscles of control and treated rats showing (A & C) glomerular capillaries (C) with regular continuous basement membranes (GBM), endothelial cells (E) and mesangial cells (MC) with dense mesangial matrix (MM), as well as normal podocytes (PC) with primary (P1) and secondary (P2) foot processes in control and TAU-treated rats, respectively. (B & D) The kidney's filtration barrier of control and TAU-treated rats, respectively appeared normal consisting of glomerular basement membranes (GBM), fenestrated endothelium (FE) and secondary foot processes (P2) separated by filtration slits (FS). (E) Congested glomerular capillaries (C) with irregularly thickened capillary basement membranes (GBM), damaged podocytes (PC) having large intraluminal vacuoles (V), hypertrophied mesangial cells (MC) with pyknotic nuclei (arrow) and expanded mesangial matrix (MM) are seen in 5-FU-treated rat. (F) The kidney's filtration barrier of 5-FU-treated rats revealed thickened, corrugated glomerular basement membrane (GBM), fused fenestrated endothelium (FE) and secondary foot processes (P2). (G) Well preserved cell structures of renal corpuscles with few dilated and congested glomerular capillaries (C) in TAU & 5-FU-treated rats. (H) Regular glomerular basement membrane (GBM), fenestrated endothelium (FE) and secondary foot processes (P2) with filtration slits (FS) of the kidney's filtration barrier of TAU & 5-FU-treated rats.

Both the histological and ultrastructural findings of the current study run parallel with those of the biochemical results as they confirm the direct toxic effect of 5-FU on the renal tissues. Treatment with 5-FU resulted in marked histopathological changes in rat kidneys and these changes were apparent in both renal corpuscles and kidney tubules. The most prominent signs of deterioration observed in the renal corpuscles were hypertrophy of the corpuscles, congestion of the glomerular capillaries and mesangial hypercellularity. Besides, other corpuscles appeared shrunken. Also, 5-FU administration revealed severe tubular

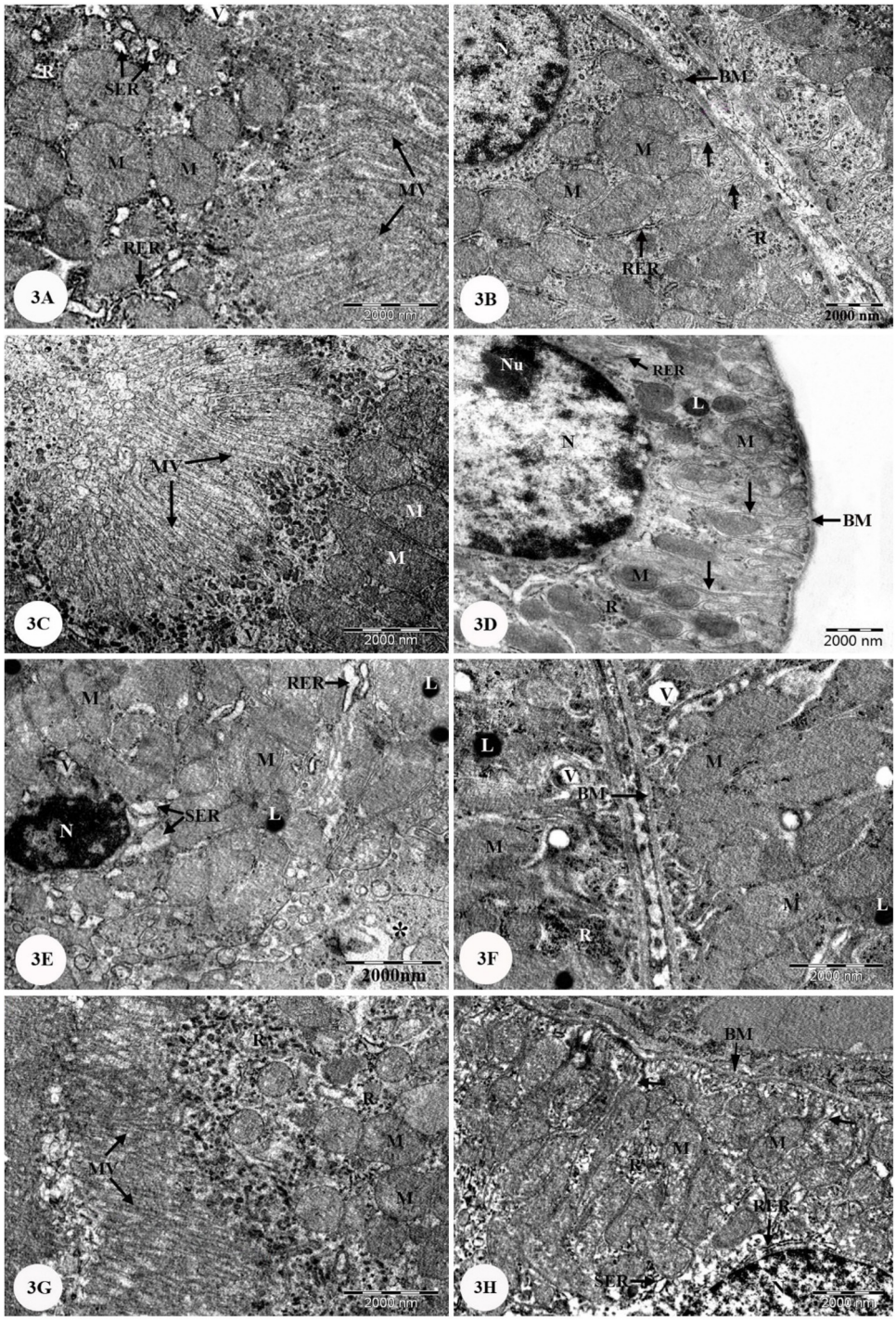

Fig. 3. Electron micrographs of the lining epithelial cells of PCTs of control and treated rats showing normal cellular ultrastructure in control (A & B) and TAU-treated (C & D) rats where the cells rest upon basement membranes (BM) with basal infoldings (arrows), the apical surfaces possess well-developed microvilli (MV), and the cytoplasm contains rounded to elongated mitochondria (M), RER, SER, free ribosomes (R), and lysosomes (L), besides intact nucleus (N) are seen. (E & F) Destructed apical microvilli (asterisk), thickened basement membrane (BM), distorted cytoplasm with an excessive number of lysosomes (Ly), increased cytoplasmic vacuoles (V), swollen mitochondria (M), hypertrophied RER and SER, as well as pyknotic nuclei (N), are seen in 5-FU-treated rats. (G & H) Nearly normal microvilli (MV), basement membranes (BM) with basal infoldings (arrows), nucleus (N), mitochondria (M), RER and free ribosomes (R) are observed in TAU & 5-FU-treated rats.

degeneration, tubular necrosis, and inter-tubular hemorrhage, beside infiltration of inflammatory cells in the peritubular and perivascular areas. In an attempt to explain these changes, Gibson and Skett (1994) stated that the kidney has significant amount of the mixed function oxidase system enzymes and prostaglandin endoperoxide synthase, two enzyme systems that have the potential to metabolically activate innocuous drugs to toxic metabolites which bind to critical, cellular macromolecules and ultimately result in necrosis of the kidney tissue. Also, Fogo et al. (2014) reported that many therapeutic and diagnostic agents may be responsible for tubular necrosis and this lesion is a dose-dependent injury with tubular cell damage normally limited to proximal tubules and usually involving almost all nephrons.

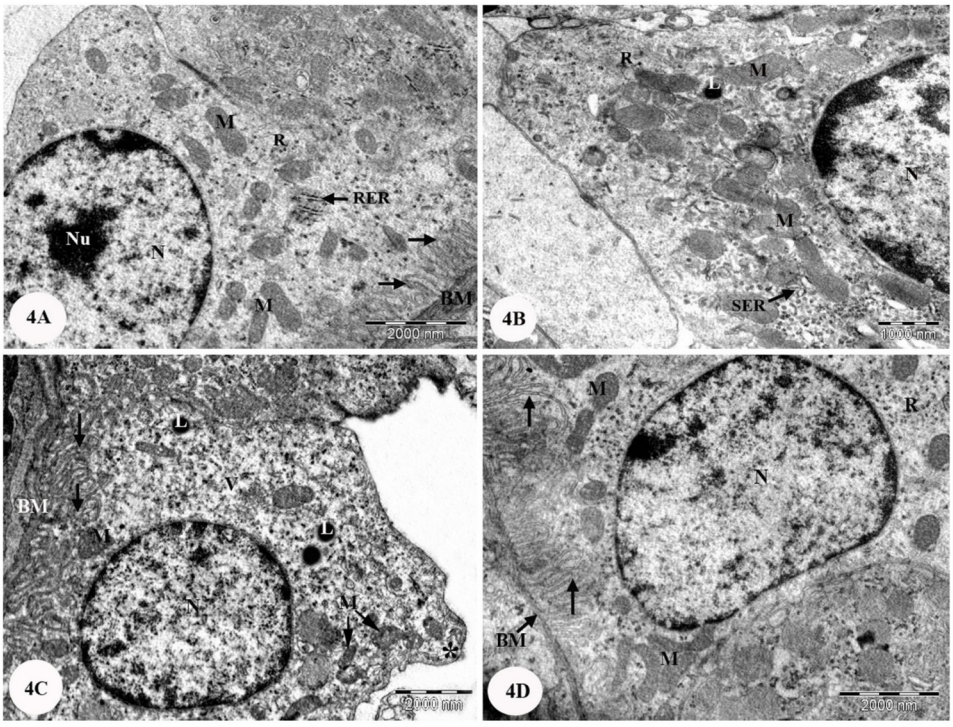

Fig. 4. Electron micrographs of the lining epithelial cells of DCTs of control and treated rats showing normal cellular ultrastructure in control (A) and TAU-treated (B) rats as they rest upon normal basement membranes (BM) with basal infoldings (arrows) and possess intact oval nuclei (N), mitochondria (M) with transverse cristae, RER, free ribosomes (R) and lysosomes (L). (C) Thickened basement membrane (BM) with irregular basal infoldings (arrows), severe cellular blabbing (asterisk), and degenerated cytoplasm with destructed mitochondria (M), increased number of lysosomes (L), vacuoles (V), as well as deformed nuclei (N) are seen in 5-FU treated rats. (D) Regular oval nucleus (N), well-organized mitochondria (M), normal basement membrane (BM) with basal infoldings (arrows) are seen in combined TAU and 5-FU treated rats.

One of the most apparent lesions observed post 5-FU administration was cellular infiltration between the renal tubules. This phenomenon was previously reported by Bianchi et al. (1999) who attributed the accumulation of inflammatory cells to the toxic effects of the drugs, since cytotoxic injury caused by drugs may lead to a chronic inflammatory response characterized by the accumulation of inflammatory cells. Also, Silva (2004) and Markowitz and Perazella (2005) mentioned that interstitial infiltration of lymphocytes, plasma cells, eosinophils, and occasionally polymorphonuclear neutrophils is an allergic hypersensitivity response. The present results are in agreement with those previously demonstrated by Chirino et al. (2004) and Behling et al. (2006) post cisplatin administration to rats.

The present ultrastructural investigation of the renal cortices of rats treated with 5-FU showed thickened and irregular glomerular basement membranes, dilated and congested glomerular capillaries, damaged lining fenestrated endothelium, hyperplasia of the mesangial cells with expansion of the mesangial matrix, and marked distortion of the podocyte's processes as some of them appeared fragmented or fused, and the others were completely lost. Such thickening and disruption of the glomerular basement membrane with widening of the glomerular capillaries may affect the mechanism of ultrafiltration, causing increased immune reaction on the basement membrane, induction of local fusion of foot processes and loss of the regular endothelial lining of the basement membrane as mentioned previously by Kulling et al. (1995). In addition, impaired glomerular filtration rate was also detected physiologically by increased serum creatinine concentration (Abdu et al., 2011).

Also, electron microscopic investigation of the renal cortices of 5-FU-treated rats showed marked ultrastructural changes of the PCTs and DCTs as revealed by irregular and thickening of the basement membrane, destruction of the apical microvilli and loss of the basal infoldings of the epithelial cells. Moreover, cytoplasmic degeneration and vacuolation, deformed mitochondria with electron dense matrices, many lysosomes, and apoptotic nuclear changes were also seen. The current results make a harmony with Kakihara et al. (2003) who emphasized that renal tubular damage is well-known renal complications caused by anticancer drugs and also with Morigi et al. (2004), Nasr and Saleh (2014) in cisplatin-treated animals.

As explained previously by Silva (2004), the renal tubular epithelial damage may be caused by either direct toxic or ischemic effects of drugs. Furthermore, Pannu and Nadim (2008) and Perazella (2009) stated that the role of the PCTs in concentrating and reabsorbing glomerular filtrate renders them vulnerable to toxicity. Besides, renal tubular cells have a high metabolic rate requiring a substantial amount of energy and their environment is relatively hypoxic causing increase the risk of hypoxic injury to the tubular cells (Perazella, 2012).

Coincided with the present biochemical results, Davies et al. (1995) and Fadel and Larkin (1996) confirmed that one of the possible mechanisms for the tubular disorders was the direct toxic effect on the cell function. They also attributed damage and deterioration of the brush borders of the PCTs to the leakages of GGT and AP enzymes that are associated with these brush borders as a result of toxin binding to them, and it is considered as an early marker of toxic tubular insult.

The current histological and ultrastructural results also revealed that most of the renal corpuscles and renal tubules restored their normal architectures in rats treated with TAU pre-, co-, and parallel with 5-FU. These results were in agreement with El-Agousa et al. (2009) who emphasized the ameliorative effect of TAU against toxemia induced by adriamycin in rats, and Das et al. (2010) who confirmed the protective role of TAU against acetaminophen-induced acute nephrotoxicity.

The exact mechanism by which 5-FU induces nephrotoxicity is not fully clear. However, one possible mechanism postulated by many investigators is free radicals' production which induces lipid peroxidation, damage of cell membrane components, activation of lysosomal enzymes and apoptosis (Kinhult et al., 2003; Xian et al., 2004). In the same context, previous studies reported that reactive oxygen species are important mediators of anticancer drug-mediated nephrotoxicity (Özen et al., 2004; Oktem et al., 2005; Parlakpinar et al., 2005). Furthermore, Evenepoel (2010) stated that the kidney is extremely susceptible to drug-induced toxicity because of its high blood flow (approximately 25% of the resting cardiac output), its capacity to concentrate drugs to levels considerably exceeding those in blood, and its ability to degrade drugs, often resulting in the formation of reactive metabolities which are increasingly believed to be critical participants in the pathogenesis of renal injury.

Administration of TAU to 5-FU-treated rats effectively mitigates the nephrotoxicity induced by this compound. This was clearly manifested by biochemical, histological and ultrastructural improvement of the kidney tissues. The protective effect of TAU supplementation against 5-FU-induced nephrotoxicity could be attributed to attenuation of the oxidative stress induced by this compound through its antioxidant effects which inhibited lipid peroxidation and neutrophil activation (Son et al., 1996). In addition to the direct antioxidant effects of TAU, it may protect cells via membrane stabilization. Timbrell et al. (1995) reported that the membrane protective effect of TAU is related to an action on membrane permeability to water and ions. Also, TAU is an osmolyte found in high concentrations in the kidney and it regulates osmotic balance and ions transport in the kidney (Trachtman et al., 1995). Both the exogenous TAU supplementation and the modulation of tissue TAU stores are known to affect renal function. Therefore, TAU therapy could benefit the dysfunctional kidneys. In harmony with the current data, previous studies have shown that TAU exerted protection against nephrotoxicity induced by gentamicin (Erdem et al., 2000), methotrexate (Çetiner et al., 2005), nicotine (Sener et al., 2005a,b,c), methiocarb (Ozden et al., 2009), aluminium chloride (Al-Kahtani, 2010) and acetaminophen (Das et al., 2010).

In conclusion, the biochemical, histological and ultrastructural findings of the present study prove that TAU has a protective effect against 5-FU-induced nephrotoxicity in adult male albino rats. This protective effect relied, at least in part, on the antioxidant and the free radical scavenging effects of TAU. Further studies are needed to explore other possible mechanisms of the protective action of TAU.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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