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Research Article

GREEN TEA (*CAMELLIA SINENSIS*) EXTRACT AMELIORATES TAMOXIFEN-INDUCED RENAL INJURY AND OXIDATIVE STRESS IN RATS

FA Mahboub[1] and WM Abdel-Wahab[2,3]

[1]Department of Biology- Faculty of Applied Science- Umm Al-Qura University - Saudi Arabia
[2]Department of Biology, College of Medicine, University of Dammam, Saudi Arabia
[3]Department of Zoology, Faculty of Science, University of Alexandria, Egypt

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ABSTRACT

Background: Tamoxifen (TAM) is a frontline therapy for treatment of hormone-dependent breast cancer. Despite its efficiency as a chemotherapeutic agent in women, its associated toxicity is well established in several organs and tissues. **Methods and Findings:** The present study was designed to investigate the protective effect of green tea (*Camellia sinensis*) extract (GTE) against renal injury induced by TAM citrate in rats. For this purpose, forty adult female rats were divided equally into 4 groups; untreated control, TAM (received 45 mg/kg/day for 7 successive days, intraperitoneal), GTE (given 1.5% w/v in water as the sole drinking fluid for 21 days), and TAM-GTE (received the same doses of both TAM and GTE). Administration of TAM induced renal dysfunction as shown by elevation in urea and creatinine levels in the serum. It also disturbed the oxidant/antioxidant status and induced oxidative stress in renal tissue. This was evidenced by augmentation of lipid peroxidation (measured as malondialdehyde, MDA) as well as depletion in the major antioxidant enzymes catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) in the kidney. Furthermore, TAM induced histopathological changes in the renal tissue. Supplementation with GTE for 21 days improved the kidney function and restored its oxidant/antioxidant balance. These biochemical findings were supported by the histological examination. **Conclusion**: In conclusion, GTE could be beneficial in attenuating TAM-induced renal injury and oxidative stress possibly due to its antioxidant properties.

INTRODUCTION

Tamoxifen (TAM) is a selective estrogen modulator that is highly recommended for treatment of hormone-dependent breast cancer. It is also a prophylactic agent for women at high risk of this cancer (Jordan, 2003; Shukla *et al.*, 2016). The therapeutic effect of TAM is attributed to its ability to bind to estrogen receptor and inhibition of proliferation of different cell types (McDonnell, 1999; Johnston, 2005). Despite its efficiency in treatment of cancer in women, the toxicity of TAM is well established in several organs and tissues (Albert *et al.*, 2004). TAM has been reported to prompt nephrotoxicity and to affect the proper kidney function (Kintzel and Dorr, 1995; Saleh *et al.*, 2016). The nephrotoxicity of TAM is related in part to its metabolites which covalently bind to DNA leading to formation of DNA adduct (Rajaniemi *et al.*, 1998). Overproduction of oxygen radicals and induction of oxidative stress are also possible mechanisms implicated in the toxicity of TAM (Dragan *et al.*, 1996; Gorin and Wauquier, 2015). The beneficial effects of TAM can be expanded through the use of an additional therapy that can abolish the adverse effects of TAM. Compounds with antioxidant properties may be useful against TAM-induced nephrotoxicity. More consideration is being paid to the beneficial effects of antioxidants extracted from plants against the toxicity of drugs especially when free radicals are involved (Frei and Higdon, 2003). Over the last three decades, green tea (*Camellia sinensis*) has attracted an increasing focus because of its health benefits. It has been reported to possess antiproliferative, antibacterial, antiviral, and chemopreventive properties (Schramm, 2013). These effects are mainly attributed to its high contents of polyphenolic compounds which have been reported to function as an antioxidant, a prooxidant, and an iron chelator (Halliwell, 2008). Catechins stand out as a major class of these polyphenolic compounds. 50%-75% of the total amount of catechins is the epigallocatechin-3-gallate (EGCG) which

Corresponding author:* **FA Mahboub
Department of Biology- Faculty of Applied Science- Umm Al-Qura University - Saudi Arabia

appears to be the most powerful ingredient of the green tea (Du *et al*., 2012). Catechins have been reported to prevent cardiovascular diseases (Forester and Lambert, 2011), protect liver and brain cells against ethanol-induced oxidative stress (Ostrowska and Skrzydlewska, 2006), and attenuate cyclosporine A-induced oxidative stress (Mohamadin *et al*., 2005). Administration of GTE as an adjunct therapy may be an appropriate approach in ameliorating TAM-induced nephrotoxicity and oxidative stress. Few studies investigated the nephrotoxicity of TAM. Therefore, the present study was undertaken to further investigate TAM nephrotoxicity and to evaluate whether the administration of GTE could have a protective effect against the biochemical, the oxidant/ antioxidant, and the histopathological alterations induced by TAM in the kidney of female rats.

MATERIALS AND METHOD

Drugs and chemicals

Tamoxifen citrate (1-[4-(2-dimethyl-aminoethoxy) phenyl]-1,2-diphenyl-1-butene) was purchased from Sigma Chemicals (St Louis, MO, USA). All chemicals and reagents used in the current study were of analytical grade.

Preparations of green tea extract (GTE)

Commercially available green tea was obtained from the local market for preparation of an aqueous extract according to Maity *et al*. (1998). The extract was prepared by soaking 15 g of instant green tea leaves for 5 min in 1 L of distilled water whose temperature did not exceed 90 ºC. The solution was filtered to obtain 1.5% GTE which was used instead of water as the sole source of drinking fluid.

Animals and experimental protocol

Forty adult female albino rats (weighing 150-170 g) were used in the experiment. They were obtained from the animal house of the High Institute of Public Health, University of Alexandria, Egypt. They were housed in wire-floored cages and maintained at controlled conditions (temperature: 25°C-27°C, air humidity: 40%-50%, and lightening: 12-hour light/12-hour dark cycle) and had free access of food and water. Animals were left to acclimatize for 1 week before the onset of the experiment. Rats were then randomly assigned into 4 groups (n=10). The first group (untreated control) had free access to drinking water and normal diet. Rats of the second group (TAM group) received TAM at a dose of 45 mg/kg/day intraperitoneal (ip) for 7 successive days (Hard *et al*., 1993). The third group (GTE group) was permitted 1.5% GTE as the sole source of drinking water for 21 days. The fourth group (TAM-GTE group) received both TAM (45 mg/kg/day, ip for 7 successive days) and GTE (1.5% as the sole source of drinking water for 7 days before TAM administration, 7 days during TAM administration, and 7 days after TAM administration). The experimental protocol of this study was in accordance with the guidelines for the use and care of laboratory animals and was approved by the local ethical committee at University of Alexandria.

Serum collection and preparation of tissue homogenate

Twenty-four hours after finishing the treatment protocol, rats were sacrificed by fast cervical decapitation under light ether anesthesia. Blood samples were collected, left to clot, and centrifuged at 3000 rpm for 15 min at 4°C to collect the serum which was stored at -20°C for further biochemical analysis. Kidneys were immediately excised from the dissected animals, trimmed of fats, and washed with physiological saline solution. One of the two kidneys was used for preparation of renal tissue homogenate as follows: 1g of the kidney tissue was homogenized in 10 mL potassium phosphate buffer containing 0.1 mM EDTA and centrifuged at 3000 rpm for 15 min. The supernatant was collected and stored at -20°C for measurement of oxidative stress parameters.

Preparation of renal tissue for histological examination

Portions of the other kidney were fixed in 10% neutral buffered formalin solution. The fixed tissues were then dehydrated, embedded in paraffin wax, sectioned at thickness of 5µm, and stained with hematoxylin-eosin (Bancroft and Gamble, 2002). Micrographs of the stained sections were taken using Olympus light microscope.

Assessment of kidney function biomarkers

The levels of creatinine and urea in serum were measured spectrophotometrically using the commercially available kits according to the manufacturer's instructions.

Determination of oxidative stress parameters in the kidney

Aliquot from the kidney homogenate was used to determine the level of Malondialdehyde (MDA) as a marker of lipid peroxidation (LPO) using the method of Ohkawa *et al*. (1979), the activity of glutathione peroxidase (GPx) as described by Tappel (1978), the activity of catalase (CAT) according to Clairborne (1985), and the activity of superoxide dismutase (SOD) according to the method of Kakkar *et al*. (1984).

Statistical analysis

Data are expressed as mean ± standard error. Statistical analysis was performed using statistical package for social science (SPSS software, version 15). Significance between the different experimental groups was determined by one-way ANOVA, followed post hoc test for multiple comparisons using the least significant digit (LSD). Significance is acceptable at P 0.05.

RESULTS

Effect on kidney function biomarkers

As depicted in Table 1, the level of urea and creatinine in the serum were significantly (p<0.001) increased (54.6% and 172.2%, respectively) in rats administered TAM. Administration of GTE as the sole source of drinking fluid induced non-significant changes in the level of these markers (GTE group). Supplementation with GTE to TAM-treated rats improved the kidney function. It completely restored the normal value of the urea when compared with the control group.

However, it partially improved the creatinine level since there is a significant (p<0.001) difference between the value in this group and both the control and the TAM-groups.

Table 1 Changes in the serum level of urea and creatinine in response to administration of TAM and/or GTE in female rats

	Control	TAM	GTE	TAM-GTE	*P*
Urea (mg/dl)	45.80 ± 2.52	70.80[a] ± 3.62	47.20 ± 3.01	49.60[b] ± 3.44	<0.001*
Creatinine (mg/dl)	0.36 ± 0.05	0.98[a] ± 0.08	0.59[a] ± 0.05	0.65[ab] ± 0.10	<0.001*

Data are presented as means ± standard error, (*n=8*). [a]Significant difference as compared to control group*P<0.05*). [b]Significant difference as compared to TAM group (*P<0.05*).
* Statistically significant at *P<0.05*.

Changes in the redox status of the kidney tissue

Changes in the renal oxidant/antioxidant status in response to TAM and/or GTE are shown in Table 2.

The activity of GPx, CAT, and SOD was decreased by 58.2%, 57.6%, and 60.3%, respectively compared with the control group.

Table 2 The effect of TAM and/or GTE on the level of MDA and the activity of CAT, SOD and GPx in of kidney homogenate of female rats

Parameter	Control	TAM	GTE	TAM-GTE	*p*
MDA (nmol/g protein)	65.6 ± 5.79	118.2[a] ± 9.62	63.0 ± 5.29	97.0[ab] ± 5.13	<0.001*
GPx (U/L)	47.8 ± 3.22	20.0[a] ± 3.10	46.80±3.90	39.0[b]±4.71	<0.001*
CAT (U/L)	36.8 ± 2.20	15.6[a] ± 1.94	36.60 ± 3.49	30.0[b] ± 3.58	<0.001*
SOD (U/L)	58.0 ± 2.65	23.0[a] ± 3.16	60.80 ± 4.20	48.80[b] ± 3.85	<0.001*
Protein (mg/g)	103.4 ± 5.63	100.0 ± 9.75	97.60 ± 7.76	100.80 ± 5.38	0.955

Data are presented as means ± standard error, (n=8). [a] Significant difference as compared to control group (*P<0.05*), [b] Significant difference as compared to TAM group (*P<0.05*). * Statistical significant at *P<0.05*.

TAM markedly enhanced LPO in renal tissue as indicated by a significant (p<0.001) increase the level of MDA (80.2%) compared with the control group. Furthermore, a significant (p<0.001) decline in the activity of the main antioxidant enzymes was detected in response to TAM administration.

Figures of: Green tea (Camellia sinensis) extract ameliorates Tamoxifen-induced renal injury and oxidative stress in rats

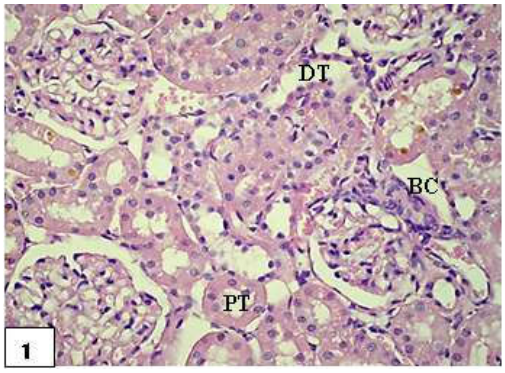

Figure 1 Photographs of control kidney section of male rat showing: Bowman's capsule (BC) with normal urinary space, proximal tubules (PT) lined with high cuboidal cells and distal tubules (DT) lined with cubical cells (H&E Stain, x40).

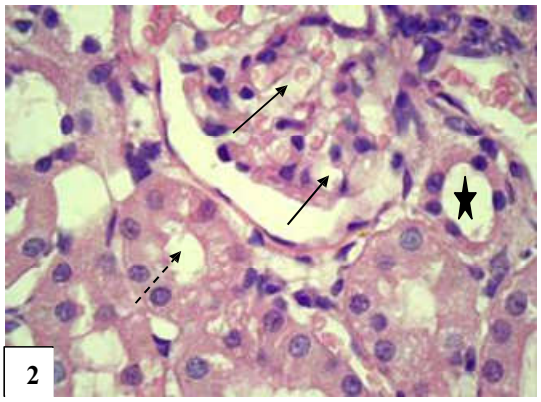

Figure 2 Enlarged part from previous figure showing: Bowman's capsule with normal capillaries (arrows), proximal tubules with narrow lumen (dashed-arrow) and distal tubules (DT) with wide lumen (star) (H&E Stain, x100).

Administration of GTE alone showed non- significant changes in MDA, GPx, CAT, and SOD when compared to the control group. It is apparent that administration of GTE to TAM-intoxicated rats ameliorated the renal LPO as evidenced by the decrease in MDA level (17.9%). It also enhanced the enzymatic antioxidants of the renal tissue as shown by the increase in the activity of GPx (95%), CAT (92.3%), and SOD (112.2%) when compared with the TAM group.

Histopathological observations

The level of serum kidney biomarkers (urea and creatinine) showed in table 1. There is significant increase in urea and creatinine levels by p < 0.001 respectively compared to the control. Administration of GTE alone showed non-significant changes in urea and creatinine level compared to control rats.

The effects of Tamoxifen administration and the modulatory activities of aqueous green tea extract on antioxidant enzymes are shown in table 2.There is significant declines in GPX, CAT and SOD enzyme levels and increase in MDA level by p < 0.001, respectively compared to the control. Administration of GTE alone showed non-significant changes in GPX, CAT, SOD enzyme levels and MDA level compared to control rats. Sections from control group (Figure 1,2) shows normal histological structure of the glomeruli and renal tubules. Green tea alone in GT -group was found to be safe and did not induce any histopathological changes in the kidney (Figure 6,7). Green tea (Figure 8, 9) reversed most of the histopathological alterations induced by TAM as seen from sections from GT+TAM group. Figure 8 shows normal glomeruli with few exception and alleviated tubular degeneration although few distal tubules filled with eosinophilic casts. The rest of histopathological changes produced by TAM were completely prevented by green tea treatment. There were no congestion of the renal tissue and no focally segmented glomerulus.

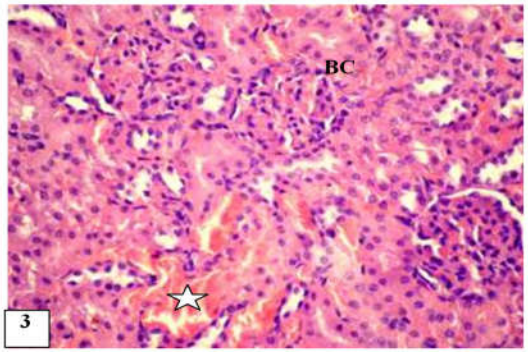

Figure 3 Photographs of TAM kidney section of male rat showing: Congested renal tissue (star), Bowman's capsule (BC) with hyper cellularity, indistinct proximal tubules and distal tubules (H&E Stain, x40).

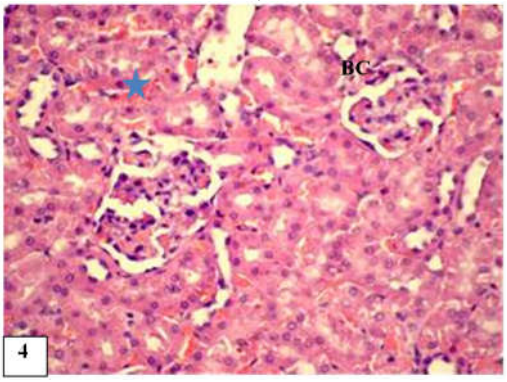

Figure 4 Photographs of TAM kidney section of male rat showing: Congested renal tissue (star), Bowman s corpuscle (BC) with focally segmented glomerulus and obstructed capillary lumens. (H&E Stain, x40).

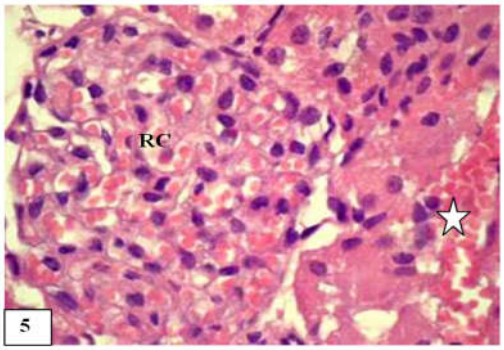

Figure 5 Photographs of TAM kidney section of male rat showing: Congested renal tissue (star), indistinct Bowman's capsule (BC) with vanished urinary space and congested capillaries (H&E Stain, x10)

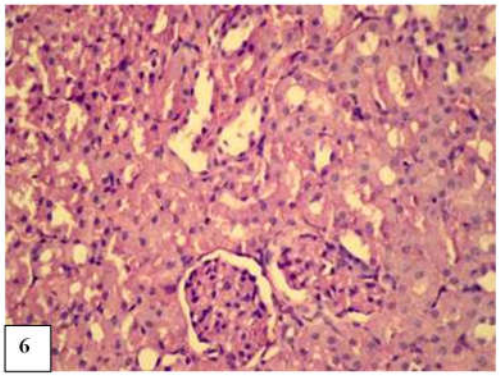

Figure 6 Photographs of GT kidney section of male rat showing: Well-organized Bowman's capsule with normal architecture of glomeruli and organized tubules (H&E Stain, x40).

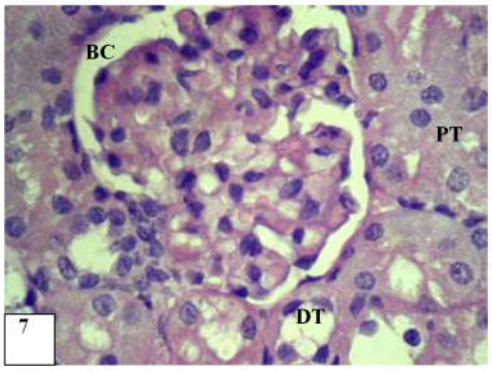

Figure 7 Photographs of GT kidney section of male rat showing: Bowman's capsule (BC) with normal urinary space, normal structures of proximal tubules (PT) and distal tubule (DT) (H&E Stain, x100).

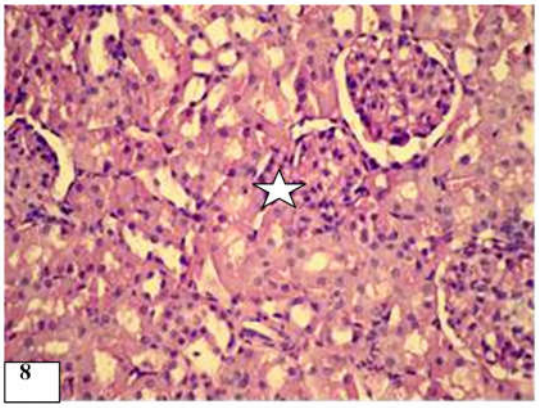

Figure 8 Photographs of GT+TAM kidney section of male rat showing: improved Bowman's capsule with infected one (star), nearly normal structures of proximal tubules and distal tubule (H&E Stain, x40).

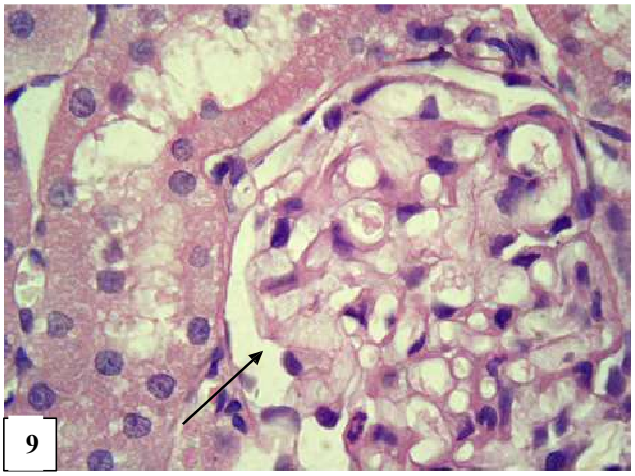

Figure 9 Photographs of GT+TAM kidney section of male rat showing: Bowman's capsule with clear capillaries and narrow space (arrow). Distal tubules (DT) with lumen filled with eosinophilic casts (H&E Stain, x100).

DISCUSSION

The use of chemotherapy for treatment of malignancy is usually accompanied by serious side effects. Tamoxifen is a frontline chemotherapeutic drug for treatment of hormone-dependent breast cancer. However, the clinical use of TAM is limited because of its toxicity. Excessive production of free radicals and its associated oxidative stress have been reported to be involved in TAM toxicity (Dragan *et al*., 1996, Gorin

and Wauquier, 2015). Therefore, supplementation with an antioxidant may be beneficial in preventing or at least reducing the side effects of TAM. Most studies reported TAM hepatotoxicity and few investigated the nephrotoxic effect of TAM. Results of our study illustrated that administration of TAM for 7 consecutive days induced signs of nephrotoxicity as evidenced by elevation in serum urea and creatinine levels. An increase in the level of LPO with a concomitant decrease in the activity of the antioxidant enzymes was detected in renal tissue. These findings were supported by the histopathological observations. Administration of GTE alleviated TAM-induced renal injury and oxidative stress, which was evidenced by the improved biochemical and oxidative stress parameters and was observed in histological examination.

Nephrotoxicity is characterized by renal dysfunction which is reflected by elevation in serum biomarkers related to kidney function (Romero *et al*., 2009). In this study, administration of TAM induced signs of nephrotoxicity as indicated by marked elevation of serum level of urea and creatinine. These results are in harmony with previous studies (Ahmed *et al*., 2008; Saleh *et al*., 2016). TAM-induced renal dysfunction may be attributed to alterations in the renal vasculature and/or damage in structures of the kidney. Changes in renal vasculature may be a result of vasoactive mediators induced by oxidative stress. These mediators may cause renal vasoconstriction and alter glomerular filtration rate which may explain the observed increase in the kidney function biomarkers (Garcia-Cohen *et al*., 2000).

Excessive generation of ROS and its subsequent increase in LPO are considered to be important mechanisms participating in many anticancer drugs-induced nephrotoxicity (Ozen *et al*., 2004; Tabassum *et al*., 2007). There is increasing evidence that TAM enhances the production of ROS which may be important mediators involved in nephrotoxicity (Nazarewicz *et al*., 2007). In the present study, renal LPO (measured as MDA) was significantly increased upon administration of TAM. These results are in agreement with previous studies (Mohamadin *et al*., 2005; Tabassum *et al*., 2007; Delwing-Dal Magro *et al*., 2016). The increase in LPO may be associated with TAM-induced release of iron ions which enhance the generation of hydroxyl radicals. These reactive species react readily with most cellular components (Ostrowska and Skrzydlewska, 2006). The increase in LPO may also be associated with poor synthesis and/or inactivation of antioxidants in the renal tissue. Administration of GTE significantly attenuated LPO indicating its ability to interfere with the oxidation of lipids. GTE has been reported to inhibit lipid and protein oxidation, preserve membrane permeability, and reduce the level of hydroxyl radicals (Seven *et al*., 2004; Chung *et al*., 2009). The mechanism behind the ameliorative effect of GTE may be related to its polyphenolic compounds which have been reported to combat the generation of free radicals and terminate LPO through various mechanisms. They are able to scavenge various free radicals which initiate LPO (Chung *et al*., 2009). Green tea polyphenols have been reported to prevent metal-catalyzed formation of radical species (Rafieian-Kopaie and Baradaran, 2013). They selectively enhance phase I and phase II metabolic enzymes and increase the formation and elimination of detoxified metabolites formed from metabolism of xenobiotic (Frei and Higdon, 2003). Epicatechins, polyphenolic antioxidant present in green tea, preserve some important endogenous antioxidants. They were found to prevent the loss of the lipophilic antioxidant α-tocopherol, and protect the antioxidant ascorbate (Skrzydlewska *et al*., 2002). Epicatechins may also be able to chelate metal ions which in turn inhibit the generation of hydroxyl radicals (Azram *et al*., 2004).

The body has its own protective mechanisms which become activated to counteract damage induced by different free radicals. Our results indicated that TAM disrupted the enzymatic antioxidants status in the kidney as reflected by the decrease in the activity of GPx, SOD, and CAT. These results are in line with Tabassum *et al*. (2007) and Saleh *et al*. (2016). This decrease may be due to decreased synthesis and/or oxidative inactivation of these enzymes. Also, the decrease in the activity of these enzymes indicates that these enzymes are being consumed in counteracting the excessive production of free radicals. El-Beshbishy (2005) mentioned that the decrease in the activities of the intracellular antioxidant enzymes in the liver of TAM-intoxicated rats may be related to increased LPO level. Supplementation with 1.5% GTE to TAM-intoxicated rats enhanced the activities of the measured antioxidant enzymes compared to TAM intoxicated rats. Similar results were reported by *Delwing-Dal Magro et al.* (2016).

Administration of TAM was found to be associated with histopathological alterations in the kidney. Glomerular congestion, narrowed Bowman`s space, periglomerular inflammation, necrosis of cells in the proximal tubules, vacuolization of cytoplasm, and epithelial desquamation were observed in response to TAM administration. Overproduction of ROS may be implicated in these histopathological changes due to damage in vasculature or other structures of the kidneys. Most of the histopathological changes induced by TAM were alleviated upon GTE administration. This could be attributed to the antioxidant capacity of GTE which reduce LPO and in turn restore the integrity of the cell membranes (Heikal *et al*., 2011). The nephroprotective effect of GTE has been previously reported by Salem *et al.* (2010) who found that administration of green tea with gentamicin showed only mild infiltrations, normal glomeruli, and alleviated tubular degeneration. Takako *et al*. (2012) suggested that green tea polyphenols are beneficial in pathological states related to oxidative stress in the kidney. GTE has been found to be beneficial against renal injury induced by cyclosporine A (Rehman *et al*., 2013), proline (Delwing-Dal Magro *et al*., 2016).

CONCLUSION

Administration of TAM to female rats induced functional impairment and histological damage in the kidney. Oxidative stress is an important mechanism involved in TAM-induced renal injury. The depletion of the renal redox system together with the liberation of free radicals in response to administration of TAM resulted in alterations in the structure of the kidney which in turn affect the proper kidney function. Administration of 1.5% GTE as the sole source of drinking fluid ameliorated TAM-induced renal dysfunction and oxidative stress. The protective effect of GTE

could be attributed to its antioxidant properties through inhibiting LPO and replenishing the activity of the antioxidant enzymes in the renal tissue. GTE may be useful as an adjunct therapy to prevent or at least attenuate TAM-induced renal injury.

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