ORIGINAL ARTICLE

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Green tea extract protects the renal cortex against bisphenol A-induced nephrotoxicity in the adult male albino rat: a histological and immunohistochemical study

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SUMMARY

Bisphenol A is a chemical used in the production of the plastic lining of food and beverage containers. As plastics are used extensively in modern life, bisphenol A is liberated into the surrounding environment. The goal of this study was to illustrate the histopathological effects of bisphenol A on the renal cortex with referral to the possible ameliorative effect of green tea extract and to throw more light on some underlying mechanisms, for the first time up to our knowledge, by which green tea extract exerted its effects against bisphenol A-induced nephrotoxicity. Forty adult male Sprague-Dawley rats were classified into four groups: Group I (control group); Group II (bisphenol A-treated group), received bisphenol by gavage 125 µg/kg once daily for 35 days; Group III (bisphenol A and green tea extract treated group), received bisphenol by gavage 125 µg/kg simultaneously with 200 mg/kg/day green tea extract once daily for 35 days; and Group IV (green tea extract treated group), received 200 mg/kg/day green tea extract for 35 days by gavage. At the end of the study, rats were anesthetized and the kidney from all groups were extracted and examined histologically and immunohistochemically. Deterioration of kidney structure was greatest in group II as compared to control group. Some of the renal corpuscles showed widening of the Bowman's capsule, shrunken degenerated glomerular tuft and dilated congested glomerular capillaries. Interstitial and intratubular hemorrhage was also observed. Moreover, there was a significant increase in the collagen deposition in bisphenol A-treated group in addition to up-regulation of inducible nitric oxide synthase (iNOS), Fas Ligand (Fas L), alpha smooth muscle actin (α-SMA) and desmin immunoreaction. The co-administration of green tea extract greatly reduced these nephrotoxic effects of bisphenol A exposure through its antioxidant, antiapoptotic and antifibrotic effects.

Key words: Kidney – Bisphenol – Oxidative stress – Fibrosis – Apoptosis – Green tea extract

INTRODUCTION

Nowadays, most of the chemicals that are used in our daily life cause hazardous effects on the environment. Some of these chemicals are severely toxic to humans. Plasticizers are among such chemicals. Plasticizers are substances that are used in disposable dishes, manufacture of polycarbonates, plastic industry, and dental materials to produce or increase plasticity and flexibility as well as to reduce fragility (Kazemi et al., 2016). Bisphenol A is an environmental chemical that has been widely used for many years in the production of polycarbonate

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plastics and epoxy resins. Because of its major applications in the production of plastic food or drink containers and the covering of food cans, people of different ages are inevitably exposed to bisphenol A in daily life (Xia et al., 2014). This has caused great fear of bisphenol A regarding human health and environmental exposure (Kamel et al., 2018).

The kidneys remove metabolic wastes from the human body and preserve fluids and electrolytes (Ross and Pawlina, 2006). The acute renal injury induced by toxins finally progresses to chronic kidney disease, which is now recognized as a global public health problem (El Nahasand Bello, 2005). Bisphenol causes oxidative stress induced tissue damage in the kidneys because it is eliminated by kidneys (Hassan et al., 2012).

Epidemiological studies showed that more than 90% of individuals tested had detectable levels of bisphenol A, providing significant evidence of ubiquitous and continuous exposure to bisphenol A even in the general population (Calafat et al., 2008). Although published data concerning occupational exposure to bisphenol A are limited and the potential for bisphenol A-related health effects among the workers is unknown, recent study showed increased urinary total bisphenol A concentrations in the group of manufacturing workers (Hines et al., 2017).

Relationships have also been reported between high serum bisphenol A levels and increased oxidative stress and inflammatory markers in hemodialysis patients using bisphenol A-containing polysulfone dialyzers (Bosch-Panadero et al., 2016).

Antioxidants are molecules that can prevent or delay the oxidation of an oxidizable substrate at low concentrations (Halliwell, 1990). Green tea (Camellia sinensis) is a worldwide consumed beverage. Its beneficial effects on health are partly due to its antioxidant, anti-inflammatory, anti- arthritic and anti-angiogenic effects. In addition, green tea is a mixture of polyphenols (the main class of active compounds) including catechins (also known as flavan-3-ols) that form about 30% (mass fraction) of green tea leaves (Castro et al., 2010).

Given that nephrotoxicity is a major public health concern, as it can progress to chronic kidney disease in the long run, it is necessary to explore whether green tea extract could alleviate the unfavorable effect of bisphenol A on the kidneys in the adult male albino rats and to elucidate, for the first time up to our knowledge, the underlying mechanisms by which the green tea extract act based on histological and immunohistochemical studies.

MATERIALS AND METHODS

Chemicals

Bisphenol A (purity > 99%): was provided from Sigma-Aldrich chemical Co., St. Louis. Mo. (USA). It was available in the form of powder.

Green tea extract: was provided from Sigma-Aldrich chemical Co., St. Louis. Mo. (USA) in the form of powder.

Experimental design

The study was conducted at the Human Anatomy and Embryology Department, Faculty of Medicine, Menoufia University. A total of forty adult healthy Sprague-Dawley rats, 10-12weeks of age, weighing 180-200 g, were used throughout the study. They were obtained from the Egyptian Organization for Biological Products and Vaccines (Cairo, Egypt). They were acclimatized for one week in stainless steel cages prior to starting the experiment. Rats were fed ad libitum by standard laboratory pellet and tap water. A 12-h light, 12-h dark cycle was maintained with optimum room temperature and humidity.

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures were conducted in accordance with the guidelines approved by the Committee of Animal Research Ethics, Menoufia University, Faculty of Medicine.

After one week of acclimatization, animals were divided randomly into four groups (n= 10 per group):

Group I (Control group): was subdivided into: GIa (plain control), where animals did not receive anything. GIb (sham control), where animals received 2 ml olive oil (a vehicle of bisphenol A) once daily orally by gavage for 35 days.

Group II (Bisphenol A treated group): Each rat received bisphenol 125 µg/kg/day (Kazemi et al., 2016) dissolved in 2 ml of olive oil orally by gavage for 35 days.

Group III (Bisphenol A and green tea extract treated group): Each rat received bisphenol 125 µg/kg/day dissolved in 2 ml of olive oil simultaneously with 200 mg/kg/day green tea extract dissolved in 1 ml of distilled water by oral gavage for 35 days.

Group IV (Green tea extract treated group): Each rat received 200 mg/kg/day green tea extract (Isbrucker et al., 2006) dissolved in 1 ml of distilled water for 35 days by gavage.

At the end of the experiment, the rats were anesthetized by inhalation of pentobarbital overdose (200mg/kg) and then sacrificed, and the kidneys were extracted.

Evaluation methods

Histological study

The kidney tissues were fixed in 10% neutral buffered formaldehyde, dehydrated through a graded alcohol series, cleared in xylene, and embedded in paraffin wax. Serial sections of 5µm were deparaffinized, hydrated, and stained with hematoxylin and eosin (H&E), for routine histological assess-

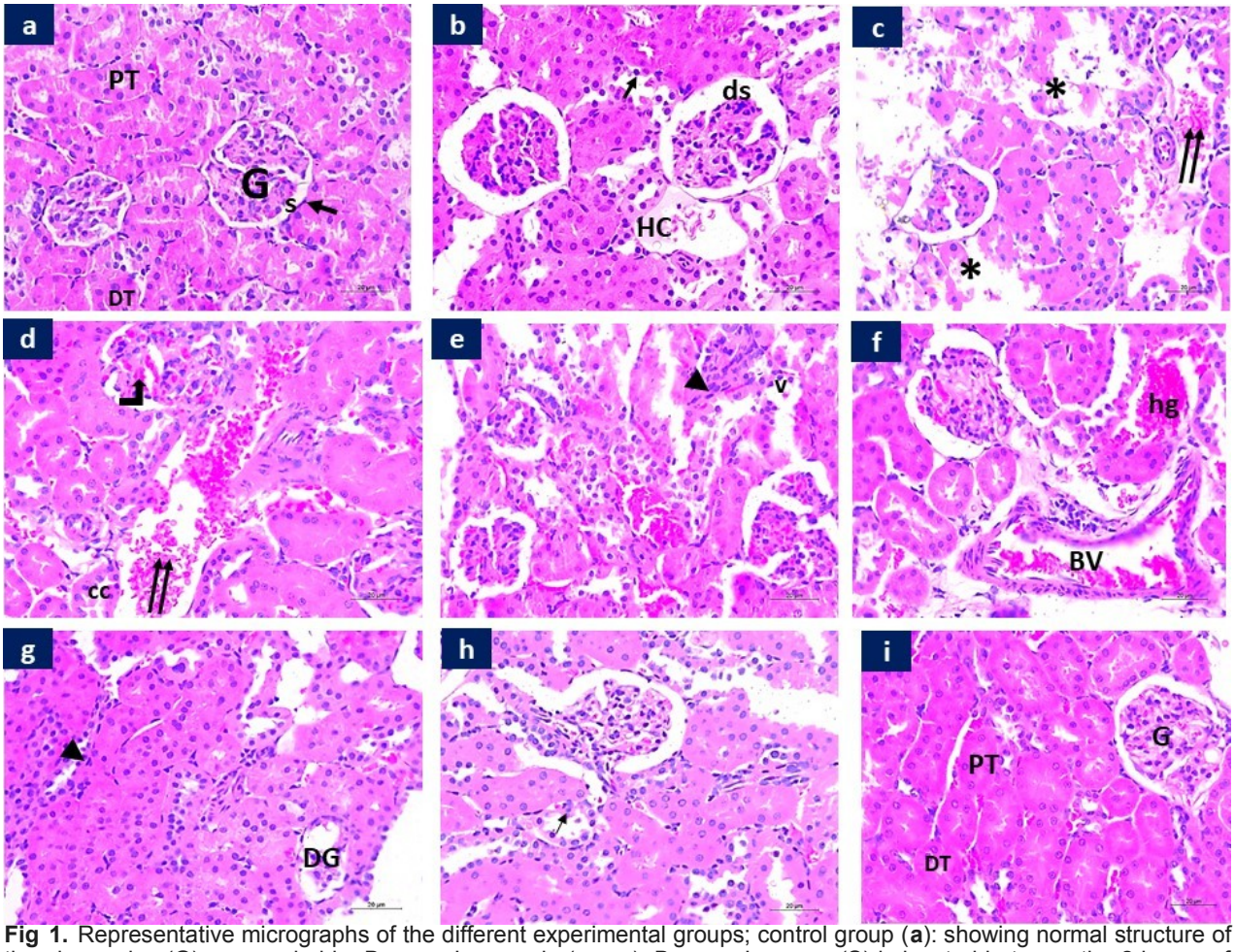

Fig 1. Representative micrographs of the different experimental groups; control group (**a**): showing normal structure of the glomerulus (G) surrounded by Bowman's capsule (arrow). Bowman's space (S) is located between the 2 layers of Bowman's capsule. Proximal (PT) and distal (DT) convoluted tubules are also seen within the renal cortex. Bisphenol-treated group (**b-h**): the renal corpuscle of this group revealing widening of the Bowman's space (ds), shrunken degenerated glomerular tuft (DG) and others showing dilated congested glomerular capillaries (bent arrow). Some renal tubules displaying exfoliating cells (thin arrow), some are with pyknotic nuclei (thick arrow), others showing vacuolated cytoplasm (V) and others are completely disrupted (asterisk). Moreover, dilated tubules with hyaline cast (HC) and cellular cast (CC) are also noted. Interstitial (double arrows), intratubular hemorrhage (hg) and dilated congested blood vessels (BV) are seen in addition to interstitial aggregation of mononuclear inflammatory infiltrates (arrow head). Bisphenol- and green-tea-treated group (**i**) showing more or less normal architecture of the renal cortex; glomerulus (G), proximal (PT) and distal (DT) convoluted tubules (H&E, Scale bar: 20 µm, 40x).

ment, and Mallory trichrome, for detection of collagen deposition, to be examined under light microscope.

Immunohistochemical study

For immunohistochemical study, the paraffin sections on poly-L-lysin coated slides were deparaffinized and rehydrated. Endogenous peroxidase was blocked by inserting the sections in 3% hydrogen peroxide (H2O2). The microwave antigen retrieval procedure was performed. The sections were incubated with primary anti-inducible nitric oxide synthase (iNOS), a marker for oxidative stress, (rabbit polyclonal, Lab vision), anti Fas-Ligand (Fas L) antibody, a marker for apoptosis, (rabbit polyclonal, Abcam), anti desmin, a marker for podocyte injury, (mouse monoclonal, Thermo Fisher Scientific Industries) and anti-alpha smooth muscle actin (α-SMA) antibody, a marker for protein of smooth muscle cells, myofibroblasts and activated fibrogenic cells, (rabbit polyclonal, Abcam), (dilution 1: 100). After that, biotinylated goat-polyvalent secondary antibody was applied. The sections were then incubated in preformed streptavidin peroxidase, and finally the prepared DAB substrate chromogen (3,3′-diaminobenzidine tetrahydrochloride) was applied and the slides were counterstained with hematoxylin to be examined under light microscope.

Morphometric study

By using Image J software, version K 1.45, the area % of collagen deposition in addition to area % of iNOS, Fas L, desmin and α-SMA immunoreaction was measured. For each parameter, ten non-overlapping fields (x 40) for every specimen from five different rats/experimental group were examined.

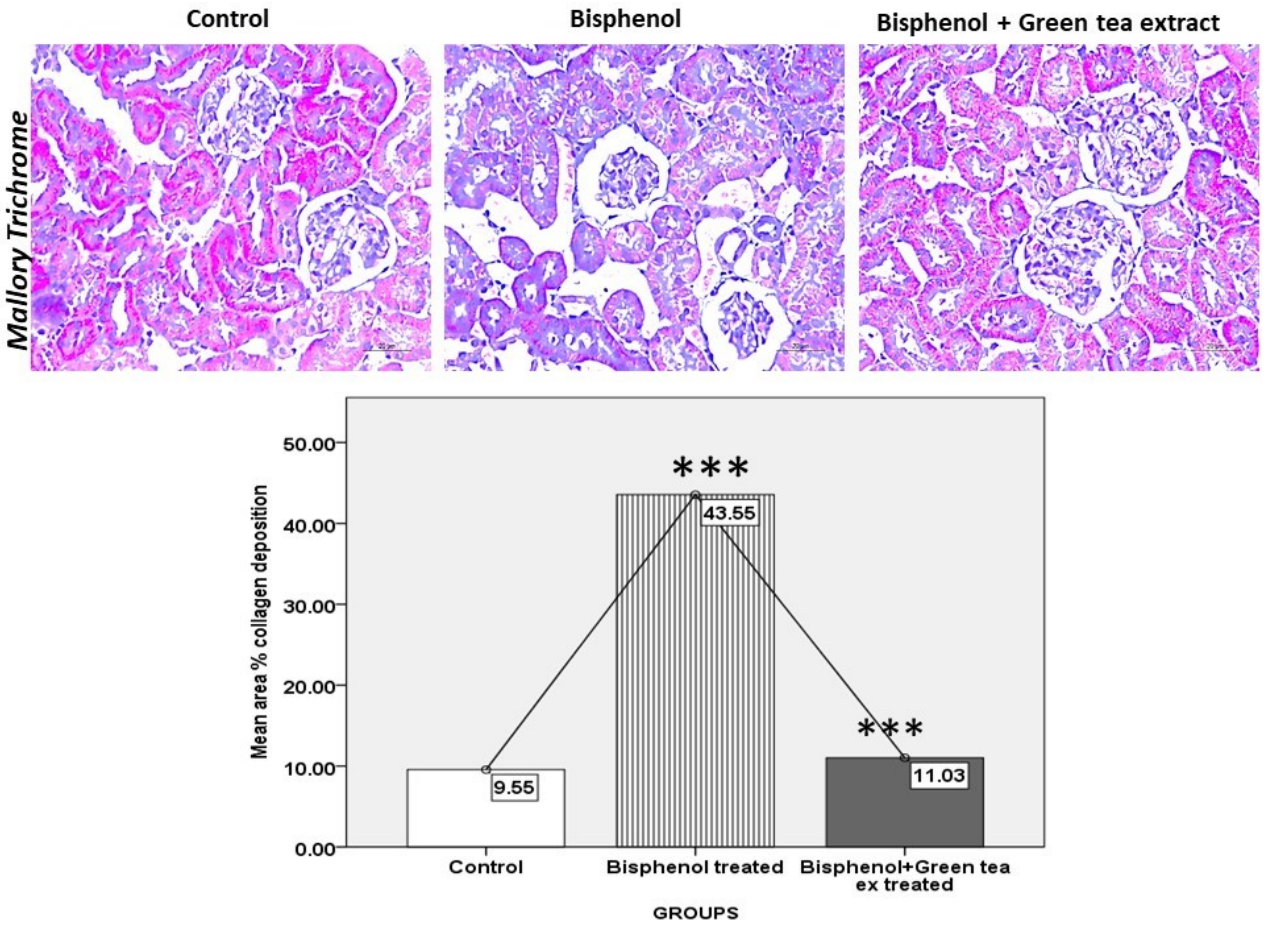

Fig 2. Representative graphs of the different experimental groups showing a significant increase in the collagen deposition within the renal cortex of the bisphenol-treated group compared to the control group and that co-administration of bisphenol and green tea extract revealing a significant decrease in collagen deposition compared to that treated with bisphenol alone. (***: P>0.001). (Mallory Trichrome, Scale bar: 20 µm, 40x).

Statistical analysis

The data were collected and analyzed using SPSS (statistical package for social science) version 23.0 on IBM compatible computer (SPSS Inc., Chicago, IL, USA). One way-ANOVA followed by post hoc Bonferroni test was employed to compare the studied groups. Data were expressed as the mean ± standard deviation (SD). A p value of < 0.05 was considered statistically significant and P value > 0.05 was considered non-significant.

RESULTS

Histological results

Hematoxylin and eosin (H&E)

Hematoxylin- and eosin-stained sections of the renal cortex in the different experimental groups were examined. The control and green tea extract group showed similar results throughout all the examined parameters. So, both are considered as a control group. The control group showed normal histological appearance of renal corpuscles (glomerular capillaries and Bowman's capsule). Between the two layers of the Bowman's capsule is the Bowman's space. In addition, proximal convoluted tubules, with basal rounded nuclei, and distal convoluted tubules, with simple cubical cells and central rounded nuclei, were also seen (Fig. 1a). In bisphenol-treated group, the renal cortex displayed variable degrees of degenerative changes. Some of the renal corpuscles showed widening of the Bowman's space, shrunken degenerated glomerular tuft and dilated congested glomerular capillaries. Moreover, there were focal areas with completely disrupted renal tubules. Some renal tubules displayed exfoliated cells with pyknotic nuclei and vacuolated cytoplasm. Dilated tubules with hyaline and cellular cast were also observed. Interstitial and intratubular hemorrhage and dilated congested blood vessels were also revealed in this group in addition to interstitial aggregation of mononuclear inflammatory infiltrates (Fig. 1 b-h). In contrast, green tea extract ameliorated the nephrotoxic effects of bisphenol and showed more or less normal architecture of the renal cortex (Fig. 1i).

Mallory trichrome

Mallory-trichrome-stained sections of the different experimental groups showed a significant in-

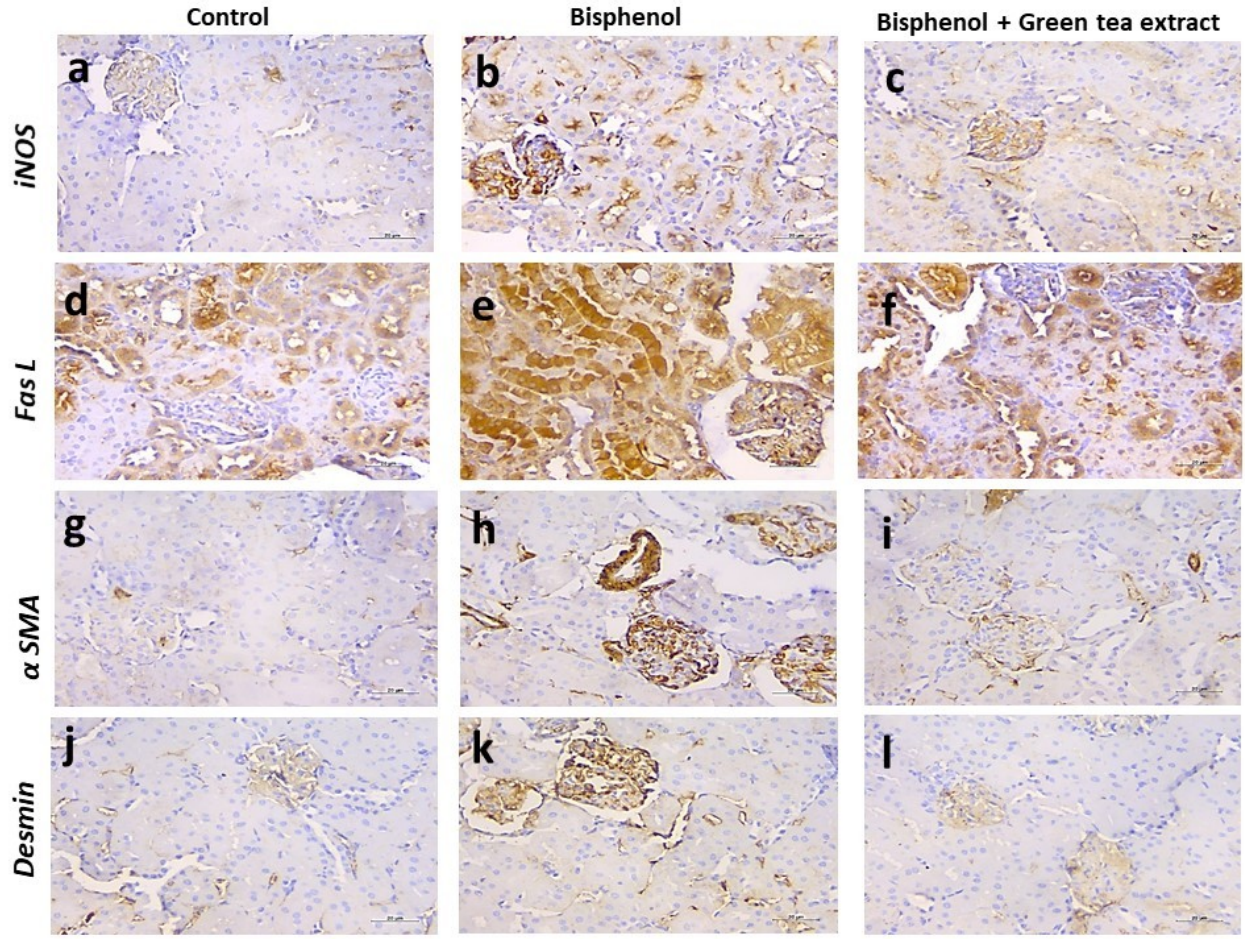

Fig 3. Representative immunostaining of rats' renal cortex of the different experimental groups revealing that co-administration of green tea extract and bisphenol significantly down regulate the immunoreaction of iNOS (a-c), Fas L (d-f), α-SMA (g-i) and desmin (j-l) compared to that treated with bisphenol only. Scale bar: 20 μm, 40 x.

crease (P>0.001) in the collagen deposition (area%) within the renal cortex of bisphenol A-treated group compared to that of control group (43.55±2.93 vs. 9.55±0.79). On the contrary, co-administration of green tea extract and bisphenol A revealed a significant decrease (P>0.001) in the area of collagen deposition when compared to the group treated with bisphenol A only (11.02±1.05 vs 43.55±2.93) (Fig. 2).

Immunohistochemical results

There was a significant up-regulation (P>0.001) of iNOS immunoreaction within the renal cortex in the bisphenol-treated group compared to the control group (27.94±1.32 vs 5.38±0.61), whereas co-administration of green tea extract and bisphenol showed a significant decrease (P>0.001) in its reaction compared to that of bisphenol-treated group (12.37±0.79 vs. 27.94±1.32) (Fig. 3a-c, Fig. 4). This was in correlation with the significant increase (P>0.001) in the Fas L immunoreaction in the bisphenol-treated group compared to the control group (43.80±1.85 vs 9.34±0.62). On the other hand, co-administration of green tea extract and bisphenol revealed a significant decrease (P>0.001) in Fas L immunoreaction compared to the bisphenol-treated group (16.47±0.99 vs. 43.80±1.85) (Fig. 3d-f, Fig. 4).

Moreover, α-SMA immunoreaction showed a significant up-regulation (P>0.001) within the renal cortex of the bisphenol-treated group compared to that of control group (12.43±0.65 vs. 1.00±0.06) that was significantly down-regulated (P>0.001) in bisphenol- and green-tea-extract-treated group compared to that of bisphenol-treated group (4.83±0.58 vs 12.43±0.65) (Fig. 3g-l, Fig. 4).

A significant up-regulation (P>0.001) of desmin immunoreaction was noted in the bisphenol-treated group compared to that of control group (12.17±1.10 vs. 2.53±0.49). On the contrary, co-administration of green tea extract and bisphenol showed a significant down-regulation (P>0.001) in its reaction compared to the bisphenol-treated group (3.68±0.51 vs. 12.17±1.10) (Fig. 3j-l, Fig. 4).

DISCUSSION

The main challenge in this study is to assess the efficacy of green tea extract in the protection against renal consequences that could result from bisphenol A. The findings that arise from this study

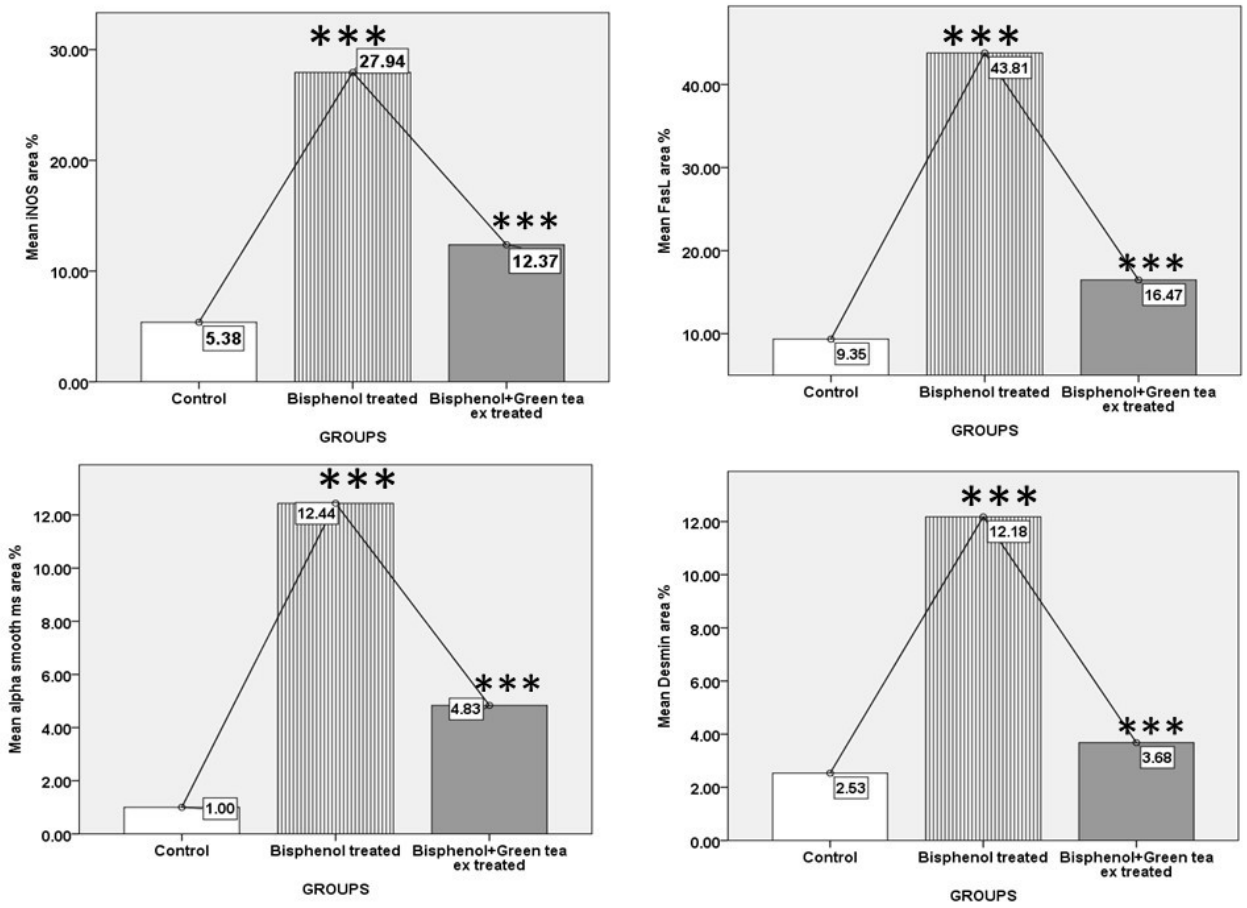

Fig 4. Histograms showing a significant increase in the area % of iNOS, Fas L, α-SMA and desmin in the bisphenol-treated group compared to the control group and that co-administration of green tea extract and bisphenol revealing a significant amelioration of these effects compared to the bisphenol-treated group. (***: P>0.001).

confirm the impact of bisphenol A in the kidney and provide a new insight regarding the potential beneficial role of green tea extract in reducing the deleterious cellular outcomes following bisphenol A exposure with referral to the underlying mechanisms.

Awareness of the environmental impact of chemical pollutants has been increased during the past few decades (Sikka and Wang, 2008). The plastic compounds can migrate to the foods that are in contact. So, the packed foods are an important source of human exposure to several phthalates (Beltifa et al., 2017). Several previous studies reported that wrapped foodstuffs are the major source of human exposure to phthalates (Kavlock et al., 2002; Fromme et al., 2007; Goulas et al., 2007). Because of widespread use of these chemicals, human exposure is inevitable (Beltifa et al., 2017).

As bisphenol A used in a wide range of daily used plastic products, it can contaminate the environment extensively either by leaching from plastic food and water containers, or as byproducts of industrialization (Helal et al., 2013). So, the food and drink are the major source of exposure (Lakind and Naiman, 2011).

The United States Environmental Protection Agency (USEPA) has established a chronic oral Reference Dose (RfD) for bisphenol A of 50 µg/kg bw/day (USEPA, 2012). However, the European Food Safety Authority (EFSA) has established a Tolerable Daily Intake (TDI) of 4 µg/kg bw/day for bisphenol A (EFSA, 2015).

Review of literature showed other studies regarding the effect of bisphenol on rat kidney such as Beenish et al. (2018), who gave bisphenol subcutaneous at a dose of 30 mg/kg/day for 30 days. In this study, a model of high dose bisphenol A exposure was studied to elucidate whether green tea extract can guard against the hazardous effect following high dose bisphenol A exposure. In our study, we tried to use the same way that a human is exposed to which is the “oral route”. For this purpose, we chose the dose used by Kazemi et al. (2016), which is 125 µg/kg/day for 35 days. Rats were preferred in this study over other animal species due to their stable genotype and ease of handling (Aitman et al., 2008).

In the present study, histological examination of bisphenol A-treated rats revealed a significant deterioration in the kidney structure manifested by glomerular atrophy, dilated congested glomerular

capillaries, interstitial and intratubular hemorrhage, polymorph nuclear leukocyte infiltration in the interstitium, and dilated congested blood vessels. This was in accordance with Sangai et al. (2012), who reported that oral administration of bisphenol A for 30 days in mice caused disorganization of the kidney glomeruli. Moreover, these results were in agreement with previous studies which showed that bisphenol is able to affect hepatic and kidney function even at very low doses (Yildiz and Barlas, 2013; Ahmed et al., 2015).

Manikkam et al. (2013) explained that the nephrotoxic effect of bisphenol is due to accumulation of its toxic metabolites and inability of the kidney to get rid of them. Such toxic substances could lead to alteration in the glomerular basement membrane and affect the glomerular filtration.

The degenerative changes observed in the kidney of bisphenol A-treated rats could be attributed to the implication of oxidative stress as confirmed in this study by the significant up-regulation of iNOS, a marker of oxidative stress. This was in accordance to Hassan et al. (2012) and Mourad and Khadrawy (2012) who suggested that pathological conditions caused by bisphenol A may be related to the generation of reactive oxygen species (ROS) and free radical by bisphenol metabolism.

Oxidative stress is an imbalance between ROS production and antioxidant defenses that cause oxidative damage (Ratliff et al., 2016). In view of renal oxidative stress, in the present study, a striking increase in the oxidant molecule nitric oxide (NO) was observed after bisphenol exposure. These findings indicate that bisphenol A-induced renal injury in this study was mediated through oxidative stress mechanism. Consistent with the current study, bisphenol A has previously been shown both in vitro and in vivo to induce oxidative injury in a variety of cells and organs as the liver (Hassan et al., 2012), testes (Takahashi and Oishi, 2003) and pancreas (Carchia et al., 2015). Also, Peerapanyasut et al. (2019) reported that repeated exposure to bisphenol led to significantly increased levels of NO and malondialdehyde with decreased levels of reduced glutathione (GSH) and superoxide dismutase (SOD) in the renal tissues.

The Fas/Fas L (Fas ligand) pathway is a key regulator of apoptosis. Fas belongs to the super family of tumor necrosis factor (TNF) receptor (Nogae et al., 1998). The present study showed that bisphenol treatment caused increased expression of Fas L in rat kidney and hence, implication of Fas pathway in renal cell apoptosis following bisphenol exposure. This was in agreement with previous studies that revealed activation of apoptosis via different pathways. Peerapanyasut et al. (2019) found significant increases in the levels of cleaved-caspase3/pro- caspase3 and Bax/Bcl-2 ratio in the kidney following exposure to bisphenol A. In accordance, Bosch-Panadero et al. (2018) demonstrated that bisphenol A causes mitochondrial injury, oxidative stress and apoptotic death in kidney tubular cells in a concentration-dependent manner. Using tunnel assay, Olea-Herrero et al. (2014) also found that both low and high bisphenol concentrations were able to induce podocyte apoptosis after 9 days in culture.

Alpha-smooth muscle actin (α-SMA) is a marker for protein of smooth muscle cells and myofibroblasts. High α-SMA expression in kidneys has been reported to be characteristic of tubular epithelial-myofibroblast trans-differentiation (Jiang et al., 2009). Expression of α-SMA is absent or only slightly detectable in the normal glomerulus, whereas it is markedly up-regulated in the mesangium during a wide range of experimental and human glomerular diseases (Macpherson et al., 1993).

In the current study, increased expression of α-SMA was detected in the kidney following bisphenol exposure compared to the control group. Dai et al. (2004) refereed the induction of α- SMA expression to mesangial cell activation, which further stimulates the deposition of the extracellular matrix and glomerulosclerosis.

Howie et al. (1995), Eddy (1996) and Geleilete et al. (2001) postulated that the progression of renal disease depends, among other factors, on the interaction between kidney cells and cytokines as transforming growth factor beta (TGF-ß) and platelet-derived growth factor (PDGF) and that these cytokines act on renal cells (tubular cells, mesangial cells and fibroblasts) by inducing proliferation and modifying their phenotypes: then these cells start to express α-SMA and increase the production of collagen and other extracellular matrix components.

Renal interstitial fibrosis is considered the hallmark of progressive renal disease. Fibroblasts and myofibroblasts are believed to be the key effector cells in renal fibrogenesis responsible for the synthesis and deposition of extracellular matrix components (Strutz and Zeisberg, 2006). This was confirmed in this study by concomitant up-regulation of α -SMA and significant increase in area % of collagen deposition indicating renal fibrosis following bisphenol exposure.

These findings were in agreement with previous studies on different organs as Elswefy et al. (2016), who reported bisphenol A induced liver fibrosis and related this to inflammatory response stimulation, along with oxidative stress, apoptotic pathway and extracellular matrix turnover activation. In accordance, Kendziorski and Belcher (2015) reported that bisphenol A exposure increases uterine gland nest formation and stromal and periglandular collagen accumulation in both CD-1 and C57Bl/6N mouse strains. Also, Kovanecz et al. (2014) showed that long-term exposure of rats to oral bisphenol A resulted in a moderate corporal

veno-occlusive dysfunction, possibly due to changes in the corporal tissue that pose transcriptional gene changes related to inflammation, fibrosis and epithelial/mesenchymal transition (EMT). Significant evidence in experimental animal models showed that the early stage of kidney glomerular damage involved injury to glomerular visceral epithelial cells (podocytes), which are specialized cells located on the outside of glomerular capillaries, forming the slit diaphragm that acts as the filtration barrier (Pavenstädt et al., 2003). It is known that podocytes have a limited ability to divide and a very limited potential for repair, so they cannot be replaced once lost (Kriz and Lehir, 2005). This in turn can result in structural damage of the cell and increased filtration barrier leakage (White and Bilous, 2004), which finally results in chronic kidney disease.

Podocytes have been shown to express the intermediate filaments desmin and vimentin. Desmin is mainly found within mesangial cells and vascular smooth muscle cells with very weak staining in podocytes (Zou et al., 2006). Therefore, desmin staining is a sensitive marker of very early podocyte injury (Gross et al., 2003).

The present study showed a significant up-regulation of desmin expression following bisphenol exposure compared to the control group indicating podocyte injury. This was in accordance with other studies that noted increased desmin staining in podocytes in many rat kidney disease models including diabetic nephropathy, Dahl salt-sensitive hypertension and age-related glomerulosclerosis (Kakimoto et al., 2014). Moreover, Olea -Herrero et al. (2014) reported that renal immunostaining with a specific podocyte marker (WT-1) showed a significant reduction in glomerular podocyte number in bisphenol injected mice. Furthermore, electron microscopy and tunel assay showed podocyte cytoplasmic enlargement as well as the presence of apoptosis, respectively. In addition, Tong et al. (2019) reported that bisphenol A exposure resulted in altered renal morphology in vivo and podocyte injury in vitro.

The beneficial effect of green tea extract against different agents' induced nephrotoxicity was studied in previous researches (Abdel-Raheem et al., 2010; Shin et al., 2012; Rehman et al., 2013). In this study the beneficial effect of green tea against bisphenol-induced nephrotoxicity was examined based on histological and immunohistochemical assessment. Co- administration of bisphenol A with green tea extract resulted in considerable amelioration of renal damage. This was in correlation with Beenish et al. (2018), who found that green tea is more beneficial than cinnamon in ameliorating the nephrotoxic effects of bisphenol A, based in their study only on routine histological examination.

Our study proved, for the first time to the best of our knowledge, that green tea extract protected the renal cortex against bisphenol-induced damage via down-regulation of iNOS, Fas-L, α-SMA and desmin immunoreaction within the renal tissue. Therefore, via the previous mechanisms, green tea extract protected the renal cortex through its antioxidant, antiapoptotic and antifibrotic effects. This was in agreement with Shin et al. (2012), who observed that green tea protected against cyclosporine-induced nephropathy through its anti-oxidative activity.

Moreover, Leung et al. (2001) stated that catechins present in green tea have antioxidant potency and enabled the kidney dysfunctions resulting from diabetes to return to normal state. In addition, green tea inhibited lipid peroxidation and induced antioxidant enzymes activity such as SOD and catalase. Green tea extract has been found to quench ROS such as singlet oxygen, superoxide and hydroxyl radicals (Das and Mukherjee, 2005).

In addition, Allam et al. (2017) examined the anti-apoptotic effect of green tea extract in a model of lipo-polysaccharide-exposure-induced liver toxicity. They suggested that the potential hepatic protective effect of green tea extract might be due to free radical scavenging potential and anti-apoptotic properties caused by the presence of polyphenolic antioxidant components. They added that the functional efficacy of green tea extract as an anti-fibrotic agent was attributed to its anti-free radical and anti-apoptotic inducing properties.

CONCLUSION

Bisphenol A causes significant changes in histomorphology of rat kidney by induction of oxidative stress, apoptosis and subsequently fibrosis. The present study shows that co- administration of green tea extract along with bisphenol A causes improvement in microstructure of the renal cortex via its antioxidant, anti-apoptotic and anti-fibrotic properties.

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