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Impact of L-Carnitine on Bisphenol A-Induced Kidney Damage in Rats

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ABSTRACT

The present study aimed to explore the protective effects of L-carnitine on the oxidative stress induced by Bisphenol A (BPA) in rat kidneys. Forty male adult rats were allocated into four groups (10 rats each); placebo, BPA (50 mg/kg bwt per os), L-carnitine (500 mg/kg bwt i.p), and the BPA/L-carnitine-treated group. After 70 days, blood and kidneys were collected for measurement of renal function, oxidative/antioxidative status, histopathological analyses, and gene expression of nrf2. BPA significantly increased serum urea and carnitine levels suggesting renal damage evidenced by hydropic degenerative changes and hydronephrosis. The level of malondialdehyde (MDA) in kidney was elevated along with decline in renal total antioxidant capacity (TAC) and reduced glutathione (GSH) concentrations following challenged with BPA. Notably, the expression of nrf2 mRNA transcript in kidney tissues was down-regulated after BPA-induced toxicity. L-carnitine treatment ameliorates the damaged effects of BPA on kidneys as indicated by low levels of serum urea and carnitine, and renal MDA. Further, L-carnitine enhances the antioxidants (TAC, and GSH), with up-regulation of nrf2 expression in kidney tissues. Our results suggest the renoprotective activity of L-carnitine in BPA-induced kidney injuries through induction of antioxidant system and modulation of oxidative stress.

1. INTRODUCTION

Bisphenol A (BPA; 2, 2-bis (4-hydroxyphenyl) propane) is a high molecular polymer organic compound widely used all over the world in the manufacture of a multitude of chemical products such as plasticizers, thermal stabilizers, pesticides, paints and dental material (Ahmed et al., 2015). In addition, it used in the production of polycarbonate and epoxy resins (Eid et al., 2015). BPA is a chemical of concern because it is an endocrine disrupter (Tsai et al., 2006) and has been associated with various adverse health effects. Exposure to BPA is thought to occur primarily through ingestion (Wilson et al., 2007), though inhalation and dermal routes may also constitute an important sources of exposure, particularly in occupational settings (Tsai et al., 2006)). Migration and leaching of BPA from metal cans to food and drinks is possible (Vandenberg et al., 2009). BPA is absorbed from gastrointestinal tract into blood and redistributed to other tissues (Fisher et al., 2011). It is highly conjugated in the liver to form bisphenol A glucuronide, a major metabolite, which is excreted in urine (Pottenger et al., 2000).

Reactive oxygen species (ROS) are cytotoxic agents causing oxidative damage by attacking cell membrane and DNA (Kabuto et al., 2003). BPA can cause liver, kidneys, brain, and other organs injury by forming ROS, which are scavenged by the endogenous antioxidant defense system (Kabuto et al., 2004). BPA shows potential acute, short-term, and sub-chronic toxicity at doses of 50mg/kg bwt and higher (Tyl, 2008).

The kidney, as well as many other tissues, has a range of antioxidant defenses including superoxide

dismutase, catalase, glutathione peroxidase, and reduced glutathione (Singh et al., 1993). In addition to these endogenous antioxidants, there are some exogenous antioxidants in cells such a L-carnitine.

Carnitine is a vitamin-like substance that is structurally similar to amino acids. Carnitine is obtained mostly from the diet. It can also be synthesized endogenously by skeletal muscle, heart, liver, kidney and brain from the essential amino acids lysine and methionine (Rebouche and Seim, 1998).

L–carnitine is a quaternary amine (4-N-trimethylammonium-3-hydroxybutyric acid) that is essential for the normal oxidation of long-chain fatty acids by mitochondria for oxidation and ATP production in peripheral tissues (Hoppel, 2003). Carnitine exists in two isomeric forms: L-carnitine and D carnitine. Only the L-isomer of carnitine is metabolically active and synthesized primarily in liver and kidney. Tissues, other than liver and kidney, are dependent on the active uptake of carnitine from blood into tissues (Deniz et al., 1999).

The kidney plays the major role in carnitine biosynthesis, excretion, and acylation, kidney contains all enzymes needed to form carnitine from trimethyl lysine in activities exceeding that of the liver (Cibulka et al., 2006), and providing a protective effect against lipid peroxidation and oxidative stress (Ye et al., 2010). The protective effect of l-carnitine on kidney tissue has been proven in various models, such as cisplatin-induced injury of the kidney and small intestine, gentamycin-induced nephrotoxicity, ischaemia–reperfusion injury of the kidney and chronic renal failure (Sener et al., 2004).

It is known that L-carnitine and its derivatives prevent the formation of reactive oxygen species, scavenge free radicals and protect cells from peroxidative stress (Izgut-Uysal et al., 2001). Furthermore, many in vitro and animal studies have reported that L-carnitine is a free radical scavenger, which protects antioxidant enzymes from oxidative damage (Kolodziejczyk et al., 2011). It has been reported that L-carnitine is a powerful antioxidant, and exerts its antioxidant effect by preventing LPO (Thangasamy et al., 2009).

This study was carried out to investigate the possible effect of BPA in rat kidneys, following oral administration, and protective effect of L-carnitine through determination of kidney function, oxidant/antioxidant indices, and histopathological findings.

2. MATERIAL and METHODS

2.1. Chemicals and Reagents

BPA was purchased from sigma chemical co, Germany. L- Carnitine was obtained from mepaco-medifood Co., Egypt. Reduced glutathione (GSH), total antioxidant capacity (TAC) and MDA kits were obtained from Bio diagnostic Co., Egypt. Kits for urea and creatinine were purchased from Vitro Scient Co., Egypt. GF-1Total RNA Extraction Kit (Vivantis, Malaysia), One-step Rotor-Gene SYBR Green RT-PCR Master Mix (Qiagen, USA).

2.2. Experimental Design

Forty adult male albino rats weighing 180 ± 200 g were obtained from Medical Research Institute, Alexandria University. The Rats were housed in stainless steel wire bottom cages with lighting cycle was 14 hr. light and 10 hr. dark with adequate ventilation. They were fed standard diet pellets and allowed food and water *ad libitum* for an acclimation period of two weeks. To investigate the toxicity of BPA, the rats were randomly divided into 4 groups of 10 rats each. Group I received 5ml/kg body weight vehicle (corn oil) by oral gavage daily. Group II treated orally with bisphenol at dose of 50 mg/kg body weight (Lam et al., 2011), dissolved in 5ml corn oil /Kg b.wt for 70 days for induction of chronic nephrotoxicity. Group III was administered daily 500 mg/kg/day of carnitine via intraperitoneal injection and group IV was administered BPA and carnitine at the same doses.

2.3. Blood collection

At the end of experimental period, rats were fasted for 12 hr, anesthetized and the blood samples were obtained from the retro-orbital sinus of the eye. The blood samples were allowed to coagulate and then centrifuged at 3000 rpm for 10 min. Sera were separated for measurement of urea & creatinine.

2.4. Tissue preparation

Immediately after blood samples were collected, animals were then sacrificed by cervical dislocation after exposure to ether and their kidneys were rapidly excised and divided into three parts; one part was immediately put at formalin 10% for histological studies, second part was kept in -80 ºC for molecular examinations. The 3rd part was weighed and homogenized, using glass homogenizer with ice-cooled saline to prepare 25% W/V homogenate. The homogenate was divided into two aliquots. The first one was deproteinized with ice-cooled 12% trichloroacetic acid and the obtained supernatant, after

centrifugation at 1000 xg was used for the estimation of reduced glutathione (GSH) content. The second aliquot was centrifuged at 1000 xg and the resultant supernatant was used for estimation level of malondialdehyde (MDA) and TAC.

2.5. Assessment of biochemical parameters

Urea and creatinine levels were determined by Talke et al., (1965) and Henry, (1964) respectively according to the manufacturer instructions. Reduced glutathione level was determined in kidney according to the method described by (Sedlack and Lindsay, 1968). The level of the lipid peroxidation end products, Malondialdehyde, which react with thiobarbituric acid-reactive substances (TBARS), was also evaluated in kidney according to the method described by Ohkawa et al., (1979). Also, TAC activity in kidney was measured as described by Koracevic et al., (2001).

2.6. Gene expression analysis of Nrf2 using RT-PCR

Total RNA was isolated from kidney tissues using GF-1 Total RNA Extraction Kit (Vivantis, Malaysia) according to the manufacturer instructions. One step quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) using SYBR Green RT-PCR Master Mix (Qiagen, USA) was performed to estimate the relative quantitative determination of the gene expression of Nrf2 mRNA level. Briefly, 12.5 µl of Rotor-Gene SYBR Green RT-PCR Master Mix, 1 of forward primer (5'-TCTCCTCGCTGGAAAAAGAA-3' for nrf2, and 5'-GGGTGTGAACCACGAGAAATA-3' for GAPDH), 1 µl of reverse primer (5'-TCTCCTCGCTGGAAAAAGAA-3' for nrf2, and 5'-AGTTGTCATGGATGACCTTGG-3' for GAPDH), 0.25 µl Rotor Gene RT mix, 2 µl RNA sample, and the reaction completed to 25 µl of nuclease free water. The real time PCR device was programmed at 55 ºC for 10 min for cDNA synthesis followed by 95 ºC for 5 min. A total of 40 cycles as the follow; 95 ºC/15s, 55 ºC/15s, 60 ºC/15s then followed by 60 ºC for 10 min. The relative expression of Nrf2 was quantified relative to the expression of the reference gene (GAPDH) in the same sample by calculating and normalizing the threshold cycles (Ct) values of target genes to that of GAPDH using ΔΔCt method.

2.7. Histopathological analyses

Instantly after sacrificing, the kidney samples were quickly preserved in 10% buffered formalin for no less than 48 hours. Thereafter, the settled examples were transformed through paraffin embedding method and were stained with hematoxylin ad eosin (H&E) according to the method described by Culling, (1983).

2.8. Statistical analysis

Statistical analysis was done by one-way analysis of variance (ANOVA). Means and standard error were also calculated according to (SAS, 2002).

3. RESULTS

3.1. Assessment of biochemical parameters

The data represented in table (1) revealed that administration of BPA at a dose of 50 mg/Kg b.wt significantly increase urea (48.9 ± 3.82) and creatinine (1.11 ± 0.10) when compared to control ones. Whereas, carnitine was non significantly increased serum urea (35.6 ± 1.33) and creatinine (0.57 ± 0.01) when compared to control ones. Interestingly, treatment of BPA-intoxicated rats with carnitine significantly decreased urea(43.3 ± 1.06) and creatinine(0.82 ± 0.05) when compared to corresponding ones in BSA-challenged rats.

Table 1: Means ± S.E of serum urea and creatinine levels in rats treated with bisphenol and/or L-carnitine.

Parameter	**Group**			
	Control	Bisphenol	Carnitine	Bisphenol + Carnitine
Urea, mg/dl	40.8 ± 2.24^{bc}	48.9 ± 3.82^{a}	35.6 ± 1.33^{c}	43.3 ± 1.06^{ab}
Creatinine, mg/dl	0.70 ± 0.04^{bc}	1.11 ± 0.10^{a}	0.57 ± 0.01^{c}	0.82 ± 0.05^{b}

Values are means ± standard errors.Means without a common superscript in a row differ significantly (P<0.05).

3.2. Effect of bisphenol and carnitine on oxidative stress and antioxidant status of rats in kidney.

The data represented in table (2) showed that administration of BPA 50 mg/Kg b.wt significantly increase renal MDA (82.0 ± 2.31) and significantly decreased GSH (16.4 ± 0.99) and TAC (4.14 ± 0.40) when compared to control ones. Whereas, carnitine significantly decreased renal MDA (54.9 ± 1.72) and significantly increased TAC (8.1 ± 0.49) when compared to control ones. Moreover, treatment of BPA-intoxicated rats with carnitine significantly decreased MDA (74.2 ± 1.63) and significantly increased both TAC (6.06 ± 0.26) & GSH (22.5 ±

0.67) when compared to corresponding ones in BSA-challenged rats.

Table 2: Means ± S.E of oxidative/antioxidant status in kidney of rats treated with bisphenol and /or L-carnitine.

	Group			
Parameter	Control	Bisphenol	Carnitine	Bisphenol + Carnitine
MDA, nmol/g	58.4 ± 2.42^{c}	82.0 ± 2.31^{a}	54.9 ± 1.72^{c}	74.2 ± 1.63^{b}
TAC, mM/L	7.64 ± 0.52^{a}	4.14 ± 0.40^{c}	8.1 ± 0.49^{a}	6.06 ± 0.26^{b}
GSH, mg/g wet tissue	26.7 ± 2.22^{b}	16.4 ± 0.99^{c}	26.6 ± 2.39^{b}	22.5 ± 0.67^{b}

Values are means ± standard errors.Means without a common superscript in a row differ significantly (P<0.05).

3.3. Molecular Findings

Gene expression of nrf2 mRNA transcript in bisphenol treated group was significantly decreased in kidney tissue as compared to control one. While, treatment of rats with carnitine significantly increased nrf2 mRNA transcript in kidney when compared with bisphenol intoxicated rats (Fig.1).

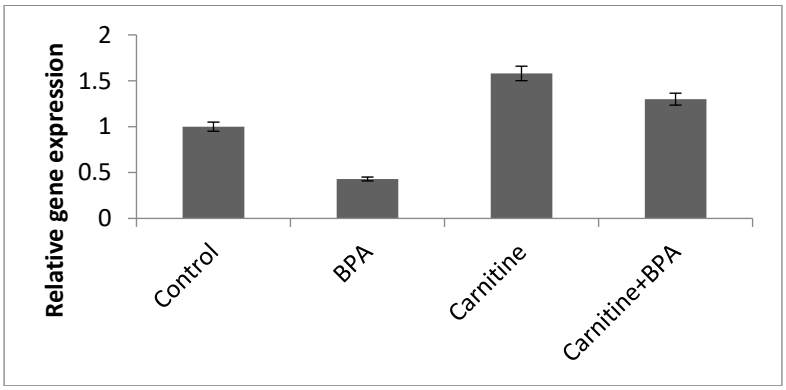

Fig.1: Relative gene expression of nrf2 mRNA transcript in Bisphenol A and carnitine treated rats

3.4. Histopathological findings

The histopathological examination of kidney of control group revealed normal renal glomeruli with normal convoluted tubules (Fig.2 A) While, BPA-treated rats showed a marked congestion of the glomeruli with degenerative changes within renal tubules and hydronephrosis (Fig. 2B). On the other hand, Carnitine -treated group revealed normal kidney histology (Fig. 2C). However, the microscopic examination of kidney tissue in (BPA+ carnitine)-treated rats showed normal glomeruli with mild to moderate vacuolation of the lining tubular renal epithelium (Fig. 2D).

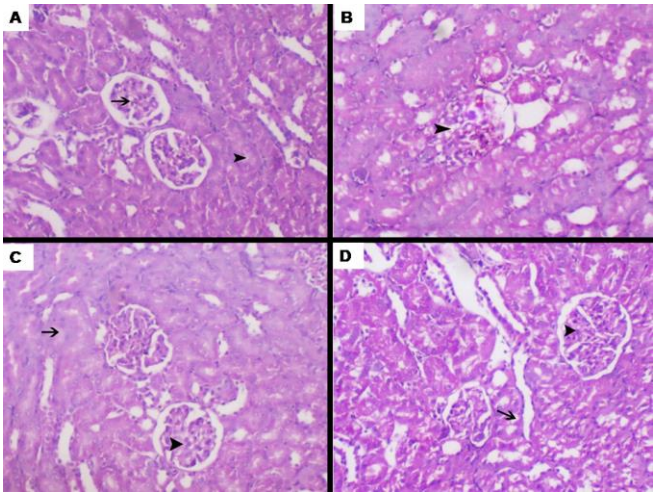

Fig. 2: (A) Kidney of control animal showing normal renal glomeruli (arrow) and tubules (arrowhead), H&E X200. (B) Kidney of bisphenol A-treated animal showing marked congestion of the glomerular tuft associated with degenerative changes within renal tubules (arrowhead), H&E X200. (C) Kidney of animal treated with L-carnitine showing normal renal glomeruli (arrowhead) and tubules (arrow), H&E X200. (D) Kidney of (Bisphenol A+ L carnitine) treated animal showing normal glomerular tuft (arrowhead) and mild to moderate vacuolation of the lining tubular renal epithelium (arrow), H&E X200

4. DISCUSSION

The present study revealed that BPA caused damage in the kidney tissues as evidenced by increase serum urea and creatine levels and altered histopathological findings. These results were in accordance with Mayssaa et al., (2017) who found that oral administration of BPA induced significant elevation in serum urea and creatinine levels compared to control one due to nephrotoxic alterations and suggested that BPA caused nephrotoxicity due to accumulation of BPA-toxic metabolites and the inability of the kidney to eliminate them which resulted in nephrotoxicity. While, Murmu and Shrivastava, (2014) showed that BPA insignificantly increased the creatinine level after 15, 30 and 60 days as compared to control. However, L-carnitine revealed significant decrease in the urea and creatinine levels as compared with control which consistent with the results of Meky et al., (2016) who assured that the use of L-carnitine in combination with gentamicin decreasing urinary excretion of total protein, serum urea, creatinine and β2-microglobulin levels. Also, Dayanandan et al., (2001) revealed that L-carnitine administration abolished the rise in plasma BUN and creatinine levels of chronic renal failure animals. Moreover, Tousson et al., (2014) revealed that the elevation caused by methotrexate in urea and creatinine levels decreased when treated by L-carnitine.

Concerning the effect of BPA and/or carnitine on oxidative/antioxidative indices in rat kidney tissues, our results revealed induction of MDA with decline in antioxidant status after BPA administration. These results were in harmony with Asahi et al., (2010) who assured that BPA increased the generation of reactive oxygen species. Also, Kabuto et al., (2003) found that BPA administration increases MDA levels in the tissue. Moreover, Morgan et al., (2014) revealed that BPA administration resulted in lipid peroxidation in kidney, brain and testicular tissues that was represented by the significantly increased MDA levels and reduced GSH concentrations. Jehane et al., (2015) stated that BPA increases the level of MDA and NO with decline in the total antioxidant capacity.

Treatment of carnitine significantly reduced MDA and activate the antioxidant status which consistent with Boyacioglu et al., (2014) who stated that renal and serum MDA decreased and GSH increased after carnitine treatment in contrast media-induced acute renal insufficiency. It has been suggested that improved GSH levels after L-carnitine addition in rats may also be attributed to increased nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) generation through increased fatty acid metabolism (Thangasamy et al .,2009). The enzyme GPx requires glutathione as a cofactor, elevation of GSH level has been observed upon carnitine supplementation in rats and this in turn, increases activity of GPx as reported earlier (Harri et al., 1986). Further, Ismail et al., (2012) stated that the administration of ginger and L-carnitine, either separately or in combination significantly increase the level of reduced glutathione. These protective effects of L-carnitine might result directly from antioxidant effects against oxygen radicals or from increased biosynthesis of enzymatic antioxidants, such as GSH and catalase (Yildirim et al., 2013).

Nrf2 (nuclear factor-erythroid 2 p45 subunit-related factor) is a master regulator of oxidative stress-inducible gene expression (Li et al., 2009). Our study revealed that gene expression of Nrf2 mRNA transcript in bisphenol treated group was significantly decreased in kidney tissue as compared to control one while, treatment of rats with carnitine significantly increased Nrf2 mRNA transcript kidney when compared with bisphenol intoxicated rats. These results were disagree with Prajakta et al., (2017) who recorded that BPA exposure increased Nrf2 gene expression.

Finally, the histopathological examination of kidney of BPA-treated group showed marked congestion of the glomeruli with degenerative changes within renal tubules and hydro nephrosis. These results in accordance with (Walaa et al., 2015) who revealed that kidney section of BPA treated rat showing severe dilatation and congestion in the cortical renal blood vessels, showing marked thickening of the glomerular and the renal tubular basement membranes. Also, Eman et al., (2013) showed that kidney tissue of rat treated with BPA showing large intertubular hemorrhagic area. Moreover, Korkmaz et al., (2009) revealed that kidney of BPA-treated groups showed congestion, necrotic area, and mononuclear cell infiltration and histopathological changes in renal tissues were observed in cortex of rats treated with BPA. On the other hand, Carnitine -treated group revealed that alternations induced by BPA were markedly reduced and improved. Tousson et al., (2014) revealed that rat kidney section in post treated group with carnitine showed moderate organized tubular and glomerular structures except mild inflammatory infiltration.

5. CONCLUSION

The present study revealed a marked renal damage evidenced by induction of oxidative stress and kidney functions with attenuation of antioxidant system following BPA administration. Carnitine act as antioxidant alleviate the damaged effect of BPA on kidneys.

6. REFERENCES

Ahmed, W.S., Moselhy, W.A., Nabil, T.M. 2015. Bisphenol A toxicity in adult male rats: hematological, biochemical ad histopathological approach. Global veterinaria. 14 (2): 228-238.

Asahi, J., Kamo, H., Baba, R., Doi, Y., Yamashita, A. 2010. Bisphenol A induces endoplasmic reticulum stress-associated apoptosis in mouse non-parenchymal hepatocytes. Life Sci. 87: 431-438.

Boyacioglu, M., Turgut, H., Akgullu, C., Eryilmaz, U., Kum, C. Onbasili, O.A. 2014. The Effect of L-Carnitine on Oxidative Stress Responses of Experimental ContrastInduced Nephropathy in Rats J. Vet. Med. Sci. 76(1): 1–8.

Cibulka, R., Široká, R., Rajdl, D., Racek, J. 2006. Asymmetric dimethylarginine as a novel independent risk factor for cardiovascular disease in hemodialysis patients. XIV International Symposium on Atherosclerosis. 18: 22-26. Roma, Italy.

Culling, C.F. 1983. Handbook of histopathological and histochemical techniques .3rd Ed. Butterworth. London.

Dayanandan, A., Kumar, P., Panneerselvam, C. 2001. Protective role of L-carnitine on liver and heart lipid peroxidation in atherosclerotic rats. Journal of Nutritional Biochemistry. 12:254–257.

Deniz, G. Karnitin: sentez, metabolizma, fonksiyon ve iskemikkalpte terapo¨tik o¨nemi. 1999. T Klin Tıp Bilimleri;19:55–62.

Tousson, E., Zaki, Z.T., Abu-Shaeir, W.A., Hassan, H. 2014. Methotrexate-induced Hepatic and Renal Toxicity: Role of L-carnitine in Treatment. Biomedicine and Biotechnology. 2 (4):85-92.

Eid, J.I., Eissa, S.M., El-Ghor, A.A. 2015. Bisphenol A induces oxidative stress and DNA damage in hepatic tissue of female rat offspring. J Basic Appl Zool 71:10–19.

Helal, E.G.E., Badawi, M.M., Soliman, M.G., Abdel-Kawi, N.A., Fadel A.E., Abozaid, M.G. 2013. Physiological and Histopathological studies on Bisphenol-A compound as xenoestrogen in male albino rats. The Egyptian Journal of Hospital Medicine. 50: 127 – 136.

Fisher, J.W., N.C. Twaddle, M. Vanlandingham and D.R. Doerge, 2011. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry ofbisphenol A in monkeys with extrapolation to humans. Toxicol. and Applied Pharmacol.257: 122-136.

Henry, R.J. 1964. Clinical Chemistry: Principles and Techniques, Harper &Row.N.Y.,287.

Hoppel, C. 2003. The role of carnitine in normal and altered fatty acid metabolism. Am. J. Kidney Dis. 41: 4–12.

Abo-Ghanema, I. I., El-Nasharty M.A., El-Far A. H., Ghonium. H.A. 2012. Effect of Ginger and L-Carnitine on the Reproductive Performance of Male Rats. World Academy of Science, Engineering andTechnology International Journal of Animal and Veterinary Sciences. 6 (4):342-351

Izgüt-Uysal, V.N., Agaç, A., Derin, N. 2001. Effect of carnitine on stress-induced lipid peroxidation in rat gastric mucosa. J Gastroenterol. 36: 231–344.

Eid, J.I., Eissa, S.M., El-Ghor, A.A. 2015. Bisphenol A induces oxidative stress and DNA damage in hepatic tissue of female rat offspring. The Journal of Basic & Applied Zoology. 71: 10–19.

Kabuto, H., Amaklawa, M., Shishibori, T .2004. Exposure to Bisphenol-A dying embryonic fetal life and reactive oxygen species in mouse tissues. Environ. Res. 93:31-35.

Kabuto, H., Hasuike, S., Minagawa, N., Shishibori, T., 2003. Effects of bisphenol A on the metabolisms of active oxygen. Environ Res. 93(1):31-5.

Kolodziejczyk, J., Saluk-Juszczak, J., Wachowicz, B. 2011. L-carnitine protects plasma components against oxidative alterations. Nutrition. 27:693–9.

Koracevic, D., Koracevic, G., Djordjevic, V., Andrejevic, S., Cosic, V. 2001. Method for the measurement of antioxidant activity in human fluids. JClin Pathol. 54(5): 356-61.

Korkmaz, A., Aydoğan, M., Kolankaya, D. Barlas, N. 2009. Vitamin C coadministration augments bisphenol A, nonylphenol, and octylphenol induced oxidative damage on kidney of rats. Environmental Toxicology, 26 (4): 325–337.

Lam, S.H., Hlaing, M.M., Zhang, X. 2011. Toxicogenomic and phenotypic analyses of bisphenol-A early-life exposure toxicity in zebrafish. PLoS ONE, vol. 6, no. 12, Article ID e28273.

Li, W., Kong, A. N. 2009. Molecular mechanisms of Nrf2-mediated antioxidant response. Mol. Carcinog. 48: 91−104.

Wahbby, M.M., Abdallah, Z.M., Abdou, H.M., Newairy, A.A. 2017.Mitigating potential of Ginkgo biloba extract and melatonin against hepatic and nephrotoxicity induced by Bisphenol A in male rats. DOI: 10.1016/j.ejbas.2017.04.004.

Morgan, A.M., El-Ballal, S.S., El-Bialy, B.E., ELBorai, N.B. 2014. Studies on the potential protective effect of cinnamon against bisphenol and octylphenol- induced oxidative stress in male albino rats, Toxicol. Rep. ,http://dx.doi.org/10.1016/j.toxrep.2014.04.003.

Murmu, S., Shrivastava, V.K. 2014. Role of Vitamin C as antidote against Bisphenol A toxicity in kidney of fresh water fish Cirrhinusmrigala (Ham) an international quarterly J. Environ. Sci. VI: 499-503.

Meky, N.H., Heibashy, M.I., Mahmoud, O.M., Mohamed, S.S., Youssef, H.A. 2016. The effect of L–carnitine on gentamicin-induced nephrotoxicity and associated anemia in adult male albino rats. Int. J. Adv. Res. 4 (4):857-870.

Ohkawa, H., Ohishi, N., Yagi, K.1979. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal. Biochem. 95: 351-358.

Pottenger, L.H., Domoradzki, J.Y., Markham, D.A., Hansen, S.C., Cagen, S.Z., Waechter, J.M. 2000. The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration. Toxicol. Sci., 54: 3-18. 8.

Prajakta, C., Shimpi, V., More, R., Paranjpe, M., Donepudi, A.C., Goodrich, J.M., Dolinoy, D.C. 2017. Hepatic Lipid Accumulation and Nrf2 Expression following Perinatal and Peripubertal Exposure to Bisphenol A in a Mouse Model of Nonalcoholic Liver Disease. Environ Health Perspect;

Rebouche, C.J., Seim, H. 1998. Carnitine metabolism and its regulation in microorganisms and mammals. Annu Rev Nutr. 18: 39-61.

Sedlak, J., Lindsay, H,R. 1968. Estimation of total protein and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal. Biochem. 25:192–205.

Singh, I., Gulati, S., Orak, J.K., Singh, A.K. 1993. Expression of antioxidant enzymes in rat kidney during ischemia reperfusion injury. Mol Cell Biochem 125:97–104.

Thangasamy, T., Jeyakumar, P., Sittadjody, S., Joyee, A. G. andChinnakannu, P. 2009. L-Carnitine mediates protection against DNA damage in lymphocytes of aged rats. Biogerontology 10:163–172.

Tsai, W. T. 2006. Human Health Risk on Environmental Exposure to Bisphenol-A: A Review. J. Environ. Sci. Health Part C. 24: 225–255.

Tyl, R.W., Myers, C.B., Marr, M.C., Sloan, C.S., Castillo, N.P., Veselica, M.M., Seely, J.C., Dimond, S.S., Van Miller, J.P., Shiotsuka, R.N., Beyer, D., Hentges, S.G., Waechter, J.M., Jr., 2008. Two-generation reproductive toxicitystudy of dietary bisphenol A in CD-1 (Swiss) mice. Toxicol. Sci : an Official Journal of the Society of Toxicology. 104: 362-384.

Vandenberg, L.N., Maffini, M.V., Sonnenschein, C., Rubin, B.S., Soto, A.M. 2009. Bisphenol-A and the great divide: a review of controversies in the field of endocrine disruption. Endocr. Rev. 30(1):75-95.

Walaa, M.S., Moselhy, W.A., Nabil, T.M. 2015. Bisphenol A Toxicity in Adult Male Rats: Hematological, Biochemical and Histopathological Approach. Global Vet. 14 (2): 228-238.

Wilson, N.K., Chuang, J.C., Morgan, M.K., Lordo, R.A., Sheldon, L.S. 2007. An observational study of the potential exposures of preschool children to pentachlorophenol, bisphenol-A, and nonylphenol at home and daycare. Environ. Res. 103: 9-20.

Ye, J., Li, J., Yu, Y., Wei, Q., Deng, W., Yu, L. 2010. L-carnitine attenuates oxidative injury in HK-2 cell via ROS-mitochondrial pathway. Regulatory Peptides., 161(1-3): 58-66.

Yildirim, R., Yildirim, A., Dane, S., Aliyev, E., Yigitoglu, R. 2013. Dose Dependent Protective Effect of L-Carnitine onOxidative Stress in the Livers of Hyperthyroid. EAJM. 45: 1−6.