

# HISTOPATHOLOGICAL AND HISTOCHEMICAL STUDY OF THE EFFECTS OF VITAMIN C ON BISPHENOL A TOXICITY IN ALBINO RATS

By

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## ABSTRACT

**Background:** The harmful effect of a phenolic type of environmental toxicant, known as bisphenol A (BPA), has achieved great relevance. The interest in this compound is increasing owing to its possible adverse effects on several organs, which has led several organizations to recommend the prohibition or at least reduction.

**Objective:** To study histopathological and histochemical changes caused by Bisphenol A in the kidney and testis of albino rats, and to identify the potential protective role of vitamin C on Bisphenol A toxicity.

**Materials and Methods:** One hundred (100) adult healthy male albino rats Western strain weighing 180 – 220 g were obtained from the animal house, Faculty of Medicine, Assiut University, Egypt, and housed in a clean capacious macro-lane cages (5 per cage which was 60x40x25 cm) under standard laboratory conditions including good aerated room with suitable temperature, relative humidity, maintained at good light with normal light/dark cycles. All rats were given normal rat diet during the experimental period with free access to water.

**Results:** Bisphenol A has deleterious effects on the histological structure of the testis and kidney of albino rats. Testis and kidney of rat administrated vitamin C in combination with Bisphenol A showed marked amelioration of the degenerative changes that were observed in rats administrated Bisphenol A alone. Effects of Bisphenol A on testis and kidney of rat after recovery for two weeks were still as in group II, while other effects become worse. The only effects which disappeared were hemorrhage and inflammatory infiltration.

**Conclusion:** BPA has many toxic adverse health effects including reproductive and renal toxicity.

**Keywords:** Bisphenol A, Vitamin C, Albino Rats.

## INTRODUCTION

Environmental pollution has become a major concern in the developed as well as under-developed countries. Approximately 70000 anthropogenic chemicals are released into the aquatic ecosystems (Ozden, 2010). Among these, there is wide ranges that shows affinity towards estrogen receptor and are structurally similar to natural or

pharmaceutical estrogens; such chemicals are now called endocrine disrupting chemicals (EDCs) (Sumpter, 2010).

Endocrine-disrupting chemicals have been the focus of scientific research. Among those, bisphenol A (BPA) is used as the monomer to manufacture epoxy, polycarbonate, and corrosion-resistant unsaturated polyester–styrene resins required for food-packaging materials in

industrial processing (*Milman et al., 2010*).

The global BPA capacity alone was reported to be 2,214,000 metric tons, with 6–10% growth in demand expected per year about 100 tons is released into the atmosphere each year (*Alonso-Magdalena et al., 2010*).

Endocrine disruptors cause adverse health effects in humans and wildlife subsequent to changes in endocrine function. BPA is among the chemicals identified as a potential endocrine disruptor based on its estrogenic properties. Studies in laboratory animals have focused on understanding the consequences of BPA for estrogenic activity, taking into account the variety of estrogen receptors (ER) and estrogen binding molecules and their functions in different reproductive processes and different stages of the life cycle. Estrogen has a pervasive effect on body function in both males and females through a variety of mechanisms. The action of BPA at ER $\alpha$ , ER $\beta$ , estrogen related receptor (ERR), and the estrogen membrane receptor (mER) has been documented (*Wetherill et al., 2011*).

Spermatogenesis is dependent on a well-orchestrated hormonal environment. Leydig cells stimulated by LH provide the local production of testosterone, and Sertoli cells stimulated by FSH provide the local production of estradiol. In addition, Sertoli cells maintain the spermatogonial stem cells responsible for the continuity of spermatogenesis. BPA exposure caused an imbalance in these hormones, which may have contributed to defects in spermatogenesis and sperm maturation (*Wisniewski et al., 2015*).

**The present work was designed to study histopathological and histochemical changes caused by Bisphenol A in the kidney and testis of albino rats and to identify the potential protective role of vitamin C on Bisphenol A toxicity.**

## **MATERIALS AND METHODS**

One hundred (100) adult healthy male albino rats western strain weighting 180 – 220 g were obtained from the animal house, Faculty of Medicine, Assiut University, Egypt and housed in a clean capacious macro-lane cages (5 per cage which was 60x40x25 cm) under standard laboratory conditions including good aerated room with suitable temperature, relative humidity, maintained at good light with normal light/dark cycles. All rats were given normal rat diet during the experimental period with free access to water.

### **Chemicals:**

1. Bisphenol A compound 99.9 % (Sigma Company).
2. Corn oil as a vehicle purchased from ARMA Co. Egypt.
3. Vitamin C (ascorbic acid) powder (Sigma Company).
4. Ethyl alcohol 100% (El Naser pharmaceutical Chemical Co., Egypt).
5. Ether anesthesia (El Naser pharmaceutical Chemical Co., Egypt).
6. Paraffin wax (El Naser pharmaceutical Chemical Co., Egypt).
7. Hematoxyline and Eosine stain (Sedico Co. Egypt).

**The animals were classified into four groups:**

- 1. Control group (vehicle control group I):** Each animal was given 1 ml of the vehicle which was corn oil orally by gavage for three months.
- 2. Treated group 1 (group II):** Each animal was given bisphenol A compound dissolved in corn oil at a dose of 320mg/kg/day orally by gavage (which represented 1/10 LD50) for 3 months.
- 3. Treated group 2 (group III):** Each animal was given bisphenol A compound dissolved in corn oil at a dose of 320mg/kg/day orally by gavage (which represented 1/10 LD50) and vitamin-C (200mg/kg/day) orally by gavage for 3 months.
- 4. Recovery group (group IV):** Each animal was given bisphenol A compound dissolved in corn oil at a dose of 320mg/kg/day orally by gavage (which represented 1/10 LD50) for 3 month only, but postponed slaughter for two weeks.

The rats were weighed at the beginning of the study, and then 2 times weekly until the end of work to calculate the dose of the drug according to the weight. At the end of this period and under ether anesthesia all animals were sacrificed after 24 hours of the last dose. The testis and kidneys were weighed and processed for examination of possible histopathological and histochemical changes.

#### **Histopathological Examination:**

#### **Processing of Paraffin sections (Drury and Wallington, 1980):**

1. The specimens were fixed in 10% buffered neutral formalin for at least 7 days.
2. Fixation was followed by dehydration in ascending grades of ethyl alcohol (50%, 70%, 96% and absolute alcohol).
3. The specimens were cleared in xylol.
4. The specimens were impregnated with soft paraffin by putting them in several changes of melted wax (melting point 50 oC) in an oven.
5. Embedding in hard paraffin was done by putting specimens in melted wax (melting point 55 oC), poured into a mold and then cooled to form paraffin blocks containing the specimens.

Serial sections 5-8 micrometers were sliced, mounted on slides and stained with Hematoxylin and Eosin stain.

#### **Histochemical Examination:**

**Masson's trichrome stain (Fawcett and Jensch, 2002):** It was valuable for distinguishing elements of connective tissue. Typically the cell cytoplasm, muscle and keratin were stained red, nuclei were black and collagen was blue. This stain benefit were from having tissue fixed using Bouin's fixative or formalin-fixation.

**Periodic acid Schiff (PAS) (Bancroft and Gamble, 2002):** This strained carbohydrates magenta, including components of the basal lamina, surface glycoproteins on cells and intracellular carbohydrates such as glycogen in hepatocytes. Cells that secreted mucus were also strongly stained (Glycogen and other carbohydrates appeared magenta, nuclei appeared blue).

## RESULTS

**Table (1) showed histopathological effects on the kidney as follow:**

Distorted glomeruli in group II (bisphenol A 320mg/kg/day), group III (bisphenol A + vitamin-C (200mg/kg/day) and group IV (recovery from bisphenol A. Narrow Bowman's space in group II, group III and group IV. Mildly edematous proximal tubular lining group II, group III and group IV. Intra-tubular casts in group

II which was average in group III due to presence of vitamin-C, group IV showed edematous /apoptotic lining of collecting tubules. Marked inflammatory infiltrate in group II which disappeared with vitamin-C in group III and after recovery in group IV. Moderate hemorrhage in group II which absent with vitamin-C in group III and disappear after recovery in group IV.

**Table (1): Histopathological changes in kidney and effects on kidney**

Parameters \ Groups	Group 1	Group II	Group III	Group IV
<b>Glomeruli</b>	0	++	++	++
<b>Bowman's space</b>	0	+	+	+
<b>Proximal tubular lining</b>	0	+	+	+
<b>Collecting tubular lining</b>	0	++	0	+
<b>Inflammatory infiltrate</b>	0	++	0	0
<b>Hemorrhage</b>	0	+	0	0

**Glomeruli:**

0= Average      += Increased cellularity      ++ = Distorted /atrophied

**Bowman's space (BS):**

0= Average      += Narrow space      ++ = very narrow/obliterated

**Proximal tubular lining:**

0 = Average lining      + = mildly edematous /apoptotic      ++ = markedly edematous/ **Necrotic**

**Collecting tubules:**

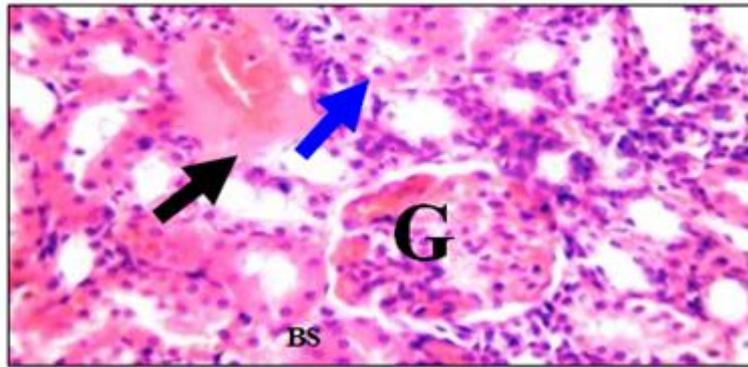
0= Average      + = Edematous /apoptotic lining      ++ = Intra-tubular casts

**Inflammatory infiltrate:**

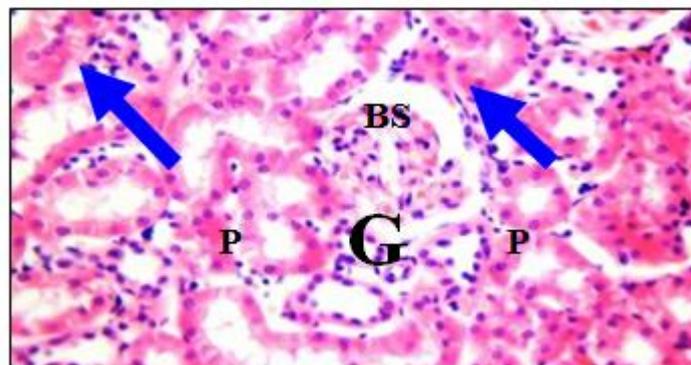
0= No infiltrate      + = Mild / moderate      ++ = Marked infiltrate

**Hemorrhage:**

0 = No Hemorrhage      ++ = Mild \ moderate      ++ = Marked



**Figure (1): (Bisphenol A):** Distorted glomerulus (G) with narrow Bowman's space (BS), proximal tubules (P) showing mildly edematous epithelial lining (blue arrow), and small area of hemorrhage (black arrow) (H&E / X 400)



**Figure (2): (Recovery from bisphenol A):** Hypocellular distorted glomerulus (G) with wider Bowman's space (BS) and proximal tubules (P) showing apoptotic epithelial lining (blue arrows) (H&E / X 400)

**Table (2): showed PAS scoring of all groups as follow:**

Mild to moderate thickening of glomerular BM in group II, group III and group IV. loss of brush border of proximal tubules in more than 10% of tubules in group II but in group III loss in less than 10% of tubules due to presence of

vitamin-C, after recovery still loss brush border of proximal tubules in more than 10% of tubules in group IV. No effects on Tubular BM all groups .control group (group 1) show average glomerular BM and tubular BM and preserve brush border of proximal tubules. (Figure 3)

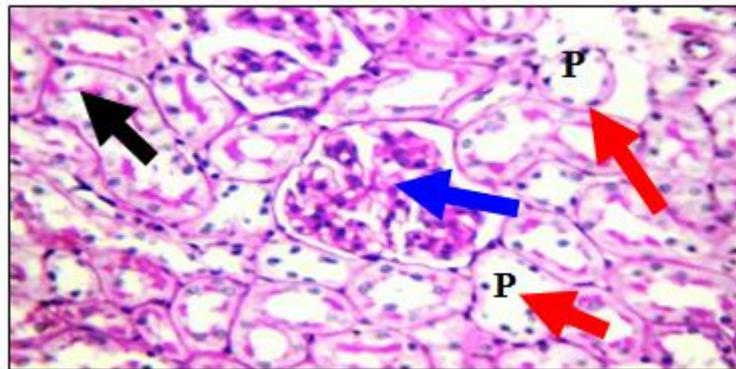
**Table (2): Scoring of all groups in kidney**

Parameters Groups	Glomerular BM	Proximal tubules		Collecting tubular BM
		Brush border	BM	
Group 1	0	0	0	0
Group II	+	++	0	0
Group III	+	+	0	0
Group IV	+	++	0	0

**Glomerular BM:** 0 = Average    + = Mild/moderate thickening    ++ = Marked thickening

**Brush border:** 0 = Preserved    + = Lost in < 10%    ++ = Lost in > 10% of tubules

**Tubular BM:** 0 = Average    + = Mild/moderate thickening    ++ = Marked thickening



**Figure (3): (Bisphenol A):** Mildly thick glomerular basement membrane (blue arrow), some proximal tubules showing preserved BM and brush borders (black arrow) and others showing loss of brush borders (red arrows) (**PAS stain / X 400**)

**Table (3):** showed Masson trichrome stain results of all groups as follow:

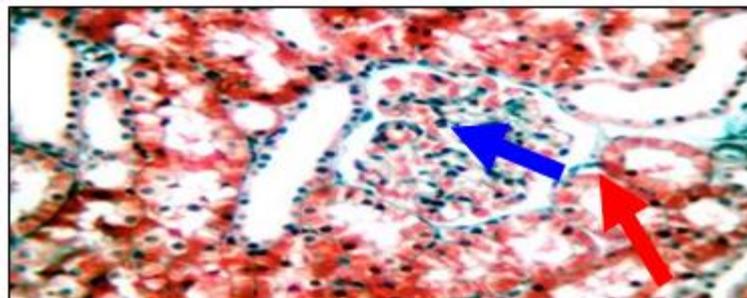
Thin irregular collagen fibers in the cortex of Group II which become thick irregular collagen fibers in Group IV after

recovery but thin regular collagen fibers (no changes) in Group III due to presence of vitamin-C. No changes on medulla in all groups. (**Figure 4**)

**Table (3):** Masson trichrome stain results of all groups

Groups	Group 1	Group II	Group III	Group IV
<b>Collagen fibers Stained deep blue</b>				
<b>Cortex</b>	-	+	-	++
<b>Medulla</b>	-	-	-	-

- - = Negative: thin regular collagen fibers
- + = Thin irregular collagen fibers
- ++ = Thick irregular collagen fibers



**Figure (4): (Bisphenol A):** Glomerular (blue arrows) and peri-tubular (red arrow) thin irregular collagen fibers (**Masson trichrome stain X 40**)

**Effects on Testis**

**Table (4): showed histopathological effects on the testis as follow:**

Mildly thick capsule in group II, while preserved (average) in group III and group IV. Sclerotic tubules in more than 10% in group II and group IV while sclerotic tubules in less than 10% in group III .

Reduced germinal lining in group II and group III, while markedly reduced in group IV. Disorganized spermatogenesis in group II and group IV, while complete in group III, and mildly separated tubules in group II, III and IV. **(Figure 6)**

**Table (4): Histopathological changes in testis.**

parameters \ Groups	Group I	Group II	Group III	Group IV
<b>Capsule</b>	0	+	0	0
<b>Tubules</b>	0	++	+	++
<b>Germinal lining</b>	0	+	+	++
<b>Spermatogenesis</b>	0	+	0	+
<b>Interstitial</b>	0	+	+	+

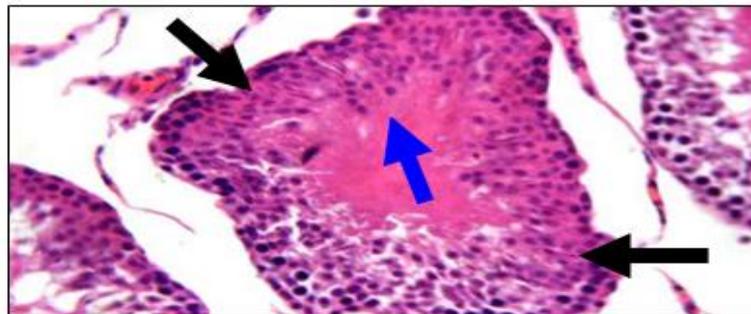
**Capsule:**  
 0 = Average                      + = Mildly thick                      ++ = Markedly thickened

**Tubules:**  
 0 = Average size    + = Distorted/sclerotic in < 10%    ++ = Distorted/sclerotic in > 10%

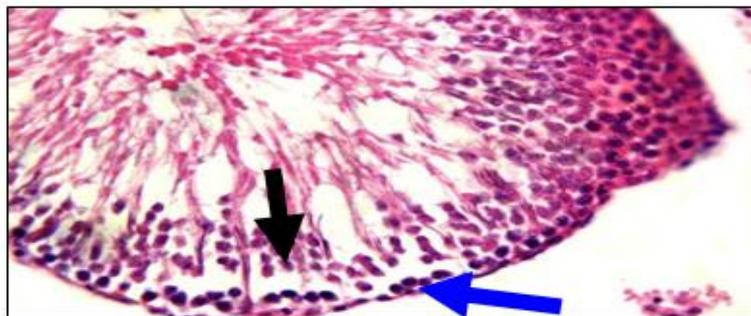
**Germinal lining:**  
 0 = Average                      + = Reduced                      ++ = markedly reduced/Atrophied

**Spermatogenesis:**  
 0 = Complete                      + = Disorganized                      ++ = No spermatogenesis

**Interstitial:** 0 = Average Interstitium    + = mildly separated tubules                      ++ = widely separated tubules



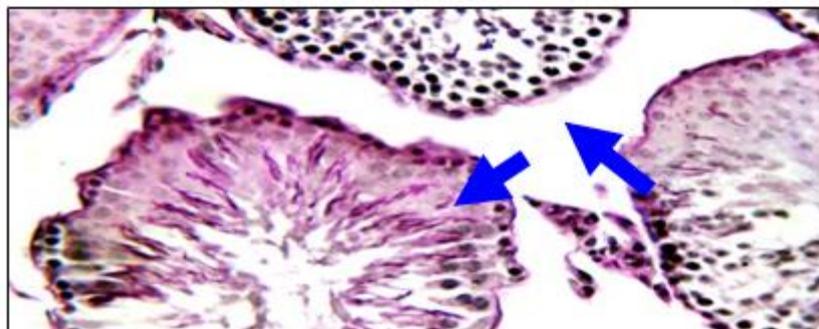
**Figure (5): (Bisphenol A): Distorted partially sclerotic tubule with marked reduction of spermatogenesis (blue arrow) and irregular basement membrane (black arrows) (H&E X / 400)**



**Figure (6): (Bisphenol A +Vit C): Average tubule with detached lining (blue arrow) and full spermatogenesis (black arrow) (H&E X 400)**

**PAS scoring of all groups: (Figure 7)**

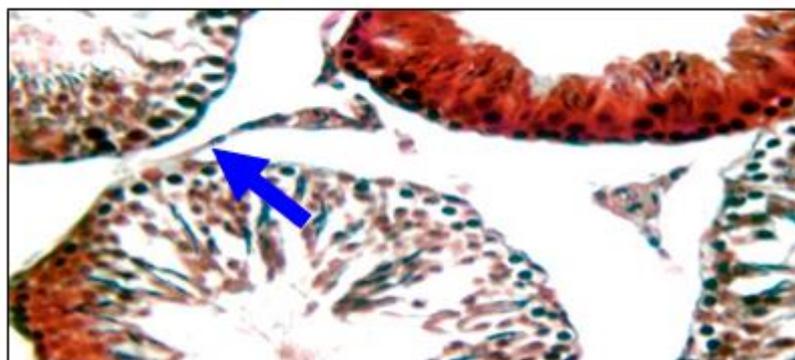
Basement membrane was mild thickened in groups II and IV while average in group III and control group.



**Figure (7): (Bisphenol A):** Testicular tissue showing mild thickening of basement membrane (blue arrows) (PAS stain / X 400).

**Masson trichrome stain results of all groups:**

Basement membrane thickened in groups II and IV, while average in group III and control group.



**Figure (8): (Bisphenol A):** Testicular tissue showing mild thickening of basement membrane (blue arrow) (Masson trichrome stain / X 400)

**DISCUSSION**

*Kortenkamp (2014)* demonstrated that BPA exposure in adults exposed to 0.02 mg/kg for 6 days compromises the daily sperm production, preventing its normal increase from 14 to 18 weeks (*Ashby et al., 2003*).

*Kourouma et al. (2014)* observed a reduction in epididymal sperm motility

and count in a dose dependent manner for the 10 and 50 mg/kg treatment groups.

In humans, a prospective study in couples undergoing medically assisted reproduction identified BPA residues in 98% of the patient urine samples, and the amount of BPA was inversely correlated with sperm concentration and motility (*Knez et al., 2014*).

BPA exposure is likely not solely responsible for modifications to human sperm parameters. The reduction in sperm production could be associated with the disruption of the spermatogenic cycle. In adulthood, BPA exposure decreases sperm count via the reduction in type A spermatogonia, spermatocytes and spermatids (*Jin et al., 2013*).

The processes of spermatogenesis begin with differentiation of spermatogonia which requires testosterone action. A study performed by *Rosnah et al. (2014)* showed significant lower level of free plasma testosterone and  $17\beta$ -oestradiol in the BPA-treated animals. It is postulated that the low testosterone level may have caused failure of spermatogenesis and disruption of the seminiferous epithelium. The low plasma testosterone level in BPA treated animals was probably due to interference of proliferative activity and development of Leydig cells in rat.

In the present study, BPA treated groups showed variable degrees of histopathological abnormalities in the testes which improved when adding vitamin C and does not change after recovery. Mildly thick capsule in group II (bisphenol A 320mg/kg/day) while preserved (average) in group III (bisphenol A + vitamin-C (200mg/kg/day) and group IV (recovery from bisphenol A). Sclerotic tubules in more than 10% in group II and group IV while sclerotic tubules in less than 10% in group III. Reduced germinal lining in group II and group III while markedly reduced in group IV. Disorganized Spermatogenesis in group II and group IV while complete in group III. Mildly separated tubules in

group II, III and IV with H&E stain. Basement membrane was mild thickened in groups II and VI while average in group III and control group (group I) with PAS stain. With Masson trichrome stain Basement membrane was thickened in groups II and VI, while average in group III and control group (group I).

*Wisniewski et al. (2015)* in their study stated that BPA exposure during adulthood: (a) reduced the total and daily sperm production by 50% at dosages of 5 mg/kg and 25 mg/kg; (b) reduced the sperm reserves in all segments of the epididymis for all BPA-treated groups by at least 70% and (c) reduced the sperm transit time in the caput, corpus and cauda epididymis by 50%.

In the present study, BPA treated groups showed variable degrees of histopathological abnormalities in the kidney which improved when adding vitamin C and does not change after recovery. With H&E stain distorted glomeruli in group II, group III and group IV. Narrow Bowman's space in group II, group III and group IV. Mildly edematous Proximal tubular lining group II, group III and group IV. Intra-tubular casts in group II which was average in group III due to presence of vitamin-C, group IV show edematous /apoptotic lining of collecting tubules. Marked inflammatory infiltrate in group II which disappear with vitamin-C in group III and after recovery in group IV. Moderate hemorrhage in group II which absent with vitamin-C in group III and disappear after recovery in group IV. With PAS stain mild to moderate thickening of glomerular BM in group II, group III (bisphenol A + vitamin-C and group IV. loss of brush border of Proximal

tubules in more than 10% of tubules in group II but in group III loss in less than 10% of tubules due to presence of vitamin-C, after recovery still loss brush border of proximal tubules in more than 10% of tubules in group IV. No effects on Tubular BM all groups, with Masson trichrome stain thin irregular collagen fibers in the cortex of group II which become thick irregular collagen fibers in group IV after recovery but thin regular collagen fibers (no changes) in group III due to presence of vitamin-C. No changes on medulla in all groups.

*Sangai et al. (2012)* stated that oral administration of BPA for 30 days caused distortion of the tubules, increased vacuolization, necrosis, disorganization of glomerulus and increased space between the glomerulus and the capsule wall. The effects were more pronounced in high-dose groups than that of low-dose groups of BPA.

In a study performed by *Sewelam and Mokhtar (2019)*, multiple degenerative changes in the renal cortex were apparently progressive through the successive postnatal weeks and became less severe at 9th PW. Glomerular necrosis, adhesion, lobulation and hypercellularity with either wide or obliterated urinary spaces were well demonstrated. In addition, proximal tubular cellular swelling with obliterated lumen, cytoplasmic vacuolization, necrosis, pyknosis, tubular dilation and intertubular congestion were observed following BPA administration.

*Hassan and Khudir (2013)* claimed that, in BPA treated rats, accumulated BPA metabolites and in ability of renal excretion might affect renal tissue with

subsequent tubular epithelial necrosis, degeneration and marked congestion.

*Abd Elghaffar et al. (2015)* concluded that exposure of rats to ACR caused testicular oxidative stress associated with histopathological changes in seminiferous tubules and reduction in testosterone in serum. Co-treatment of rats with garlic oil ameliorate the toxicity of ACR in rat testes by alleviating LPO and NO through scavenging of free radicals and enhancing the activity of SOD and CAT and GSH level.

In a study performed by *Sangai et al. (2012)*, cotreatment of quercetin (which is a potent antioxidant found in various fruits and vegetables) and BPA caused significant mitigation in morphological alterations, body weight as well as absolute and relative weights of liver and kidney compared with only BPA-treated groups.

The administration of vitamin C to nephrotoxic rat's dose dependently increases plasma vitamin C concentrations, and thus, the resistance of plasma to lipid peroxidation. Plasma and body saturation with vitamin C at high dose in rats appears desirable to maximize tissue antioxidant protection and lowers the risk of oxidative damages in gentamicin nephrotoxicity (*Derakhshanfar et al., 2013*).

Exposures of Bisphenol-A and supplement of vitamin-C showed recovery in hepatic cells, interrenal cells and uriniferous tubules as compared to Bisphenol-A group. These showed that vitamin-C denotes as antidote against Bisphenol toxicity in *Cirrhinus mrigala* (*Murmu and Shrivastava, 2011*).

## CONCLUSION

BPA has many toxic adverse health effects including reproductive and renal toxicity. Histopathological and histochemical study with H&E, PAS and Masson stains of testicular and renal tissues of albino rats administered BPA and vitamin C suggesting the important role of vitamin C on minimizing hazards of Bisphenol A.

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دراسة التأثيرات النسيجية المرضية والكيميائية لتأثير فيتامين  
سى على سمية البسفينول أ في جرذان التجارب البيضاء  
محمد نافع السيد، مجدى محمد شريف، ناجى محمد الفضالى، أشرف إبراهيم حسن،  
سيد عبد الرحيم سيد\*

قسمى الطب الشرعى والسموم الإكلينيكية، الباثولوجيا العامة\*، كلية الطب، جامعة الأزهر

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**خلفية البحث:** البسفينول أ هو عبارة عن مركب صناعى مكون من  
تكاتف مجموعتين من الفينول وجزئ اسيتون واحد.

**الهدف من البحث:** دراسة التغيرات الكيميائية والنسيجية التي يسببها  
البسفينول أ في الكلى وخصية الجرذان البيضاء ولتحديد الدور الوقائي  
المحتمل لفيتامين سى على سمية البسفينول أ.

**المواد وطرق البحث:** أجريت الدراسة على عدد مائة من ذكور  
الجرذان البالغة والتي تراوح وزنها من 180 إلى 220 جرام , وقد تمت  
رعايتها فى بيت الحيوان بكلية الطب بجامعة أسيوط، وتم وضعها في  
أقفاص نظيفة واسعة النطاق (5 لكل قفص) تحت ظروف المختبر  
القياسية بما في ذلك غرفة جيدة التهوية مع درجة حرارة مناسبة ،  
ورطوبة نسبية ، يتم الحفاظ عليها في ضوء جيد مع دورات الضوء /  
الظلام الطبيعية. أعطيت جميع الفئران غذاء طبيعي للجرذان خلال فترة  
التجربة مع حرية الوصول إلى الماء.

**نتائج البحث:** مادة البسفينول أ لها تأثير خطير على كل من الخصية  
والكلى وأحدثت تغيرات فى شكل الخلايا. وقد أدى تعاطى فيتامين سى  
بالتزامن مع مادة البيسفينول أ إلى الحد من الأثار الضارة التي تحدثها  
هذه المادة على الخلايا. وظلت هذه التأثيرات الضارة موجودة حتى بعد

التعافى من مادة البيسفينول أ لمدة أسبوعين بل إن بعض التأثيرات ازداد  
سوءا .

**الإستنتاج:** مادة البسفينول أ لها العديد من الآثار الصحية الضارة السامة  
بما في ذلك السمية الإنجابية والكلوية.

**الكلمات الدالة :** البسفينول أ ، فيتامين سى ، جردان التجارب البيضاء.