

Protective Effect of Taurine Against Bisphenol A -Induced Hepatotoxicity in Albino Rats

Esam Mohamed Abd- Allah, Maha Abd El Hameed Hilal,
Doha Saber Mohamed, Azza Omar Hassan*, Ahmed Mohamed Said
Department of Forensic Medicine and Clinical Toxicology and Histology,
Faculty of Medicine, Sohag University, Egypt

*Corresponding author: Azza Omar Hassan, Mobile: 01000532969, Email: azzamahmoud559@yahoo.com

ABSTRACT

Background: Bisphenol A (BPA) is one of the most utilized industrial chemicals worldwide. It is commonly found in a variety of consumer products. Taurine is a natural product; has been shown to protect cells against the cytotoxic effects and inflammations associated with oxidative stress and provide anti-inflammatory effects.

Objectives: This study was designed to investigate the toxic effects of BPA on the liver and evaluate the possible protective effect of taurine.

Methods: Forty adult male albino rats were divided equally into four groups (10 rats per group). Group I: Rats fed on basal diet and distilled water. Group II: Received taurine orally (100 mg /kg /day). Group III: Rats treated orally with bisphenol (130 mg /kg /day). Group IV received BPA and taurine. After one month, all animals were sacrificed and blood was collected for analysis.

Results: There is increased serum AST& ALT level and histopathological changes in liver. Toxic effects declined markedly with taurine co-administration.

Conclusions: The present study concluded that BPA has many toxic effects on liver, taurine has a potential protective effect against such harmful effects.

Keywords: BPA, Taurine, Alanine transaminase (ALT), Aspartate transaminase (AST), liver.

INTRODUCTION

Bisphenol A (BPA) is one of the major materials used to produce polycarbonate plastic, epoxy resin, health care products, and thermal resistant products ⁽¹⁾. BPA began to be predominantly used as a monomer to manufacture polymers, such as Polycarbonates (PCs), epoxy resins, polysulfone and polyacrylate ⁽²⁾.

Currently, PC plastics used to produce optical materials. Also used to manufacture electronic equipment, bottles, reusable plastic bottles, dishes, bowls, cups, microwavable utensils, and food containers ⁽³⁾. Epoxy resins are used to protect canned food and beverages and as a surface coating on drinking water storage tanks. Due to the broad application of BPA, exposure of the general population to BPA can occur via a range of products ⁽⁴⁾.

Exposure to this chemical is ubiquitous, and occurs mostly via the oral (approximately 90%), respiratory, and dermal routes in human and animals ⁽⁵⁾.

Harmful effects of BPA in cells and tissues mostly mediated by increased oxidative stress associated with an elevated production of toxic free radicals ⁽⁶⁾. Exposure to BPA is linked to cardiovascular disease, brain development abnormalities, obesity, hypertension, thyroid dysfunction, diabetes, breast cancer and infertility ⁽⁷⁾. Oxidative stress is a condition that disturbs the oxidant/antioxidant balance as a result of a significant rise in reactive oxygen species (ROS) in cells and a decline in antioxidant levels ⁽⁸⁾.

Taurine is a sulfur-containing b-amino acid (2-aminoethane sulfonic acid) that is abundant in the cells of many tissues ⁽⁹⁾. The primary mechanisms of taurine cytoprotection is its antioxidant activity, which is

mediated by: First, taurine is a proven anti-inflammatory agent that neutralizes the neutrophil oxidant, hypochlorous acid, also interferes with the inflammatory process ⁽¹⁰⁻¹¹⁾. Second, taurine diminishes the generation of superoxide by the mitochondria ⁽¹²⁾.

It also was found that taurine has emerged as an attractive therapeutic agent against liver injury as it is actively involved in the reduction of hepatic oxidative burst, which is accompanied by a remarkable increase in anti-oxidant enzymes and by attenuation of inflammatory injury ⁽¹³⁾.

MATERIAL AND METHOD

Animals:

The experimental procedure was conducted in accordance with the guide of the care and use of laboratory animals approved by the Medical Research Ethics Committee of Faculty of Medicine, Sohag University. The study was conducted on 40 adult male albino rats weighing (200± 20 gm). The animals were housed in animal house, Faculty of Medicine, Sohag University, in metal cages under ambient temperature, 21± 3 °C. Animals were fed with standard pellet food and water. They were acclimatized to the laboratory condition for one week before starting the treatment protocol. The study was performed at December 2020.

Experimental design:

Animals groups: The rats were divided randomly into 4 groups, 10 animals each:

- **Group I (Control group):** Rats fed on basal diet and distilled water.

- **Group II (Taurine group):** Rats treated orally with taurine at dose of 100 mg /kg /day, dissolved in distilled water, for one month (14, 15).
- **Group III (Bisphenol A group):** Rats treated orally with bisphenol A 130 mg /kg /day (1/25 of LD50) (14, 15), dissolved in distilled water(16), for one month. The oral LD50 of bisphenol A in rats is 3250 mg\kg (17).
- **Group IV (Bisphenol A & Taurine group):** The rats were treated with taurine at dose 100 mg/kg/day orally followed after 1 hour by bisphenol A at dose 130 mg /kg /day for one month. At the end of the study: Rats were sacrificed by cut throat under light anesthesia. Blood samples were collected after slaughtering for analysis (liver enzyme). Necropsy was done for all animals; liver was taken for histopathological examination with light microscopy.

The research was approved by the Medical Research Ethics Committee of Faculty of Medicine, Sohag University.

METHOD

1- Blood samples : 2 ml of blood were drawn from each rat from cervical blood vessels during slaughtering; blood samples were placed in a tube containing heparin anticoagulant for liver enzymes.

2 -Tissue samples : Necropsy was performed for all groups. The livers from all animals were fixed in formalin 10% and paraffin embedding. Five µm sections were cut and stained with hematoxylin and eosin then examined by light microscope for the evaluation of any pathological changes and then photographed.

Statistical analysis

All statistical procedures were computed using Statistical Program for Social Science (SPSS), version 16.0 computer software. SPSS inc. Chicago, USA. All data were presented as mean± SD and compared by Student’s t-test and one way ANOVA test. P value < 0.05 was considered as significant.

RESULTS

I- Biochemical results:

I.1.Results of level of ALT enzyme:

There was a significant statistical increase in the mean values of ALT in group III (112.30 mg/ml) as compared to group I and group II (26.1 IU/l and 21.38 IU/l). As shown in table (1) and graph (1). Where p-value was (< 0.001 and < 0.001) respectively. As shown in Table (2), there was no significant statistical difference in the mean value of ALT in group IV (25 IU/l) as compared to group I and group II (26.1 IU/l and 21.38 IU/l respectively).

Table (1) and graph (1) showed significant statistical decrease in the mean values of ALT in group IV (25 IU/l) as compared to group III (112.30 IU/l). Where p- value was (< 0.001) as illustrated in table (2). There was a significant statistical difference in the mean

value among all studied groups as P- value was (< 0.001) as illustrated in Table 2.

Table (1): The mean values and standard deviation of serum ALT IU/l and serum AST IU/l in the studied groups

	ALT	AST
Groups	Mean ± SD*	Mean ± SD*
Group 1	26.10 ± 4.68	53.90 ± 12.63
Group 2	21.38 ± 2.92	87.10 ± 11.63
Group 3	112.30 ± 22.36	137.50 ± 17.60
Group 4	25.00 ± 5.43	47.30 ± 11.41

*SD: Standard deviation *ALT: Alanine transaminase *AST: Aspartate transaminase.

Table (2): The statistical difference of serum ALT IU/l in the different studied groups using one way ANOVA test and post-hoc Tukey HSD test

Groupsp	*P value by TUKEY's Test	*P value by ANOVA
I Versus II	0.809	<0.001***
I Versus III	<0.001***	
I Versus IV	0.997	
II versus III	<0.001***	
II versus IV	0.902	
III versus IV	<0.001***	

* p-values: ** < 0.01 :Highly significant *** < 0.001 : Very highly significant *ANOVA : Analysis of variance.

* ALT: Alanine transaminase.

I.2.Results of level of AST enzyme:

Table (1) and graph (2) revealed a significant statistical increase in the mean values of AST in group III (137.50 IU/l) as compared to group I and group II (53.9 IU/l and 87.1 IU/l). The p - value was <0.001 and <0.001) respectively, as illustrated in table (3). There was no significant statistical difference in the mean values of ALT in group IV (47.10 IU/l) as compared to group I (53.90 IU/l).

Table (3): The statistical difference of serum AST IU/l in the different studied groups using one way ANOVA test and post-hoc Tukey HSD test

Groups	*P value by TUKEY's Test	*P value by ANOVA
I Versus II	<0.001***	<0.001***
I Versus III	<0.001***	
I Versus IV	0.805	
II versus III	<0.001***	
II versus IV	<0.001***	
III versus IV	<0.001***	

* p-values: ** < 0.01 Highly significant *** < 0.001 Very highly significant *ANOVA : Analysis of variance *AST: Aspartate transaminase

There was significant statistical decrease in the mean values of ALT in group IV (47.10 mg/ml) as compared to group II (87.100 IU/l) as shown in table (1) and graph (2). The p - value was (<0.001) as shown in table 3. There was a significant statistical decrease in the mean values of AST in group IV (47.10 IU/l) as compared to group III (137.50 IU/l) as shown in table 1 and graph 2. The p - value was (<0.001) as shown in table 3. There was a significant statistical increase in the mean values of AST in group II (87.100 IU/l) as compared to group I (53.90 IU/l) as illustrated in table 1 an graph 2. There was a significant statistical differences in the mean value among all the studied groups as The p - value was (<0.001) as shown in table 3.

II. Histopathological results of the study groups:

Light microscopic examination from liver sections of group I & II showed similar results. In the

liver sections stained with hematoxylin and eosin (H&E).

The hepatocyte plates in the hepatic lobules were radiating from the central vein to the periphery and the blood sinusoids were present in between. The hepatocytes had acidophilic vacuolated cytoplasm with vesicular nucleus and some of them were binucleated (Fig. A). Hematoxylin and eosin stained sections from liver of group III (130 mg/kg BPA) revealed dilation and congestion of blood sinusoids some hepatocytes appeared less acidophilic with pyknotic nuclei others appeared with enlarged one (Fig., B). In some animals the endothelium of the central appeared detached, the hepatocytes appeared shrunken deeply stained. Von kupffer cells were prominent (Fig., C).

The liver sections of group IV (100mg/kg of taurine &130mg/kg BPA) appeared more or less as the control group (Fig., D).

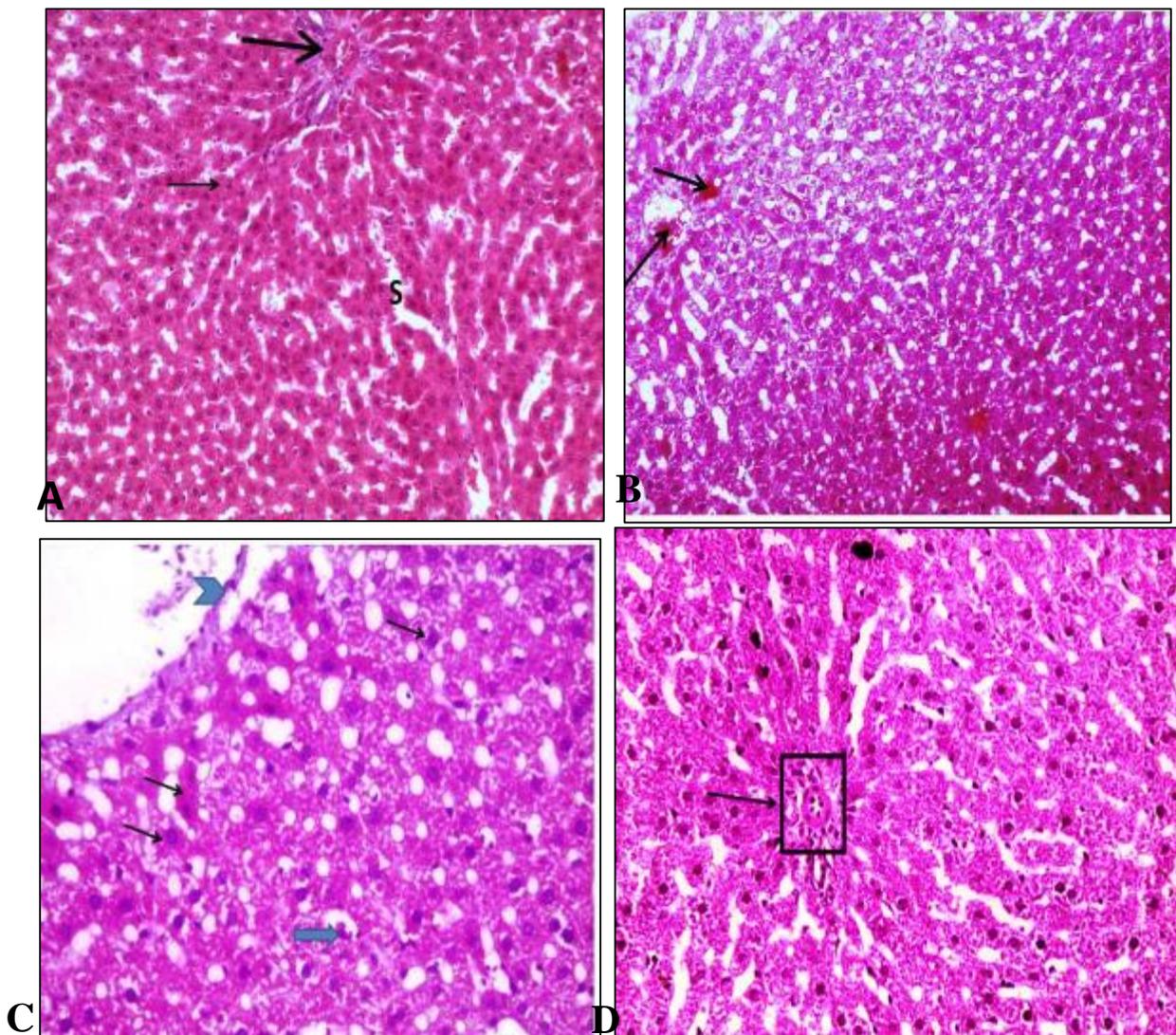


Fig. (A): A photomicrograph of liver section showing, the portal area (thick arrow) , hepatocyte (thin arrow) and blood sinusoids (S) (**Group I & II x 200 H&E**). **Fig. (B):** A photomicrograph of liver section showing dilated congested blood sinusoids (arrow) (**Group III bisphenol**) x 200 H&E. **Fig. (C) :** A photomicrograph of liver section showing, detached endothelium of the central vein (arrow head) shrunken deeply stained hepatocyte with pyknotic nuclei (thin arrow) and prominent Von kupffer cells (blue arrow)(**Group III bisphenol A**) x 400 H&E. **Fig. (D) :** A photomicrograph of liver section of showing , portal area (arrow) ,the hepatic architectue is more or less as the control group (**Group IV bisphenol + taurine**) x 400 H&E.

DISCUSSION

BPA is one of the most utilized industrial chemicals worldwide. It is commonly found in a variety of consumer products, especially in those of polycarbonate plastics and epoxy resins. Many studies have found that BPA is widely found in food, the environment, and even human body fluids⁽¹⁸⁾. A large number of *in vivo* and *in vitro* experiments have demonstrated that BPA can accumulate and affect several important organ functions, including testis, brain, heart, liver and pancreas⁽¹⁹⁾. Taurine is involved in bile formation. It is a natural compound found in animal tissues. It has significant biological functions like membrane stabilization, modulation of calcium signaling, osmoregulation and antioxidant activity⁽²⁰⁾.

In the present study, there was a significant statistical increase in the mean values of serum ALT and AST in group III compared to control group. There was no significant statistical difference in the mean value of ALT and AST in group IV as compared to group I and group II. While, there was significant statistical decrease in the mean values of ALT and AST in group IV as compared to group III. This means that serum level of ALT and AST, in animal groups that ingested toxic dose of BPA without taurine ingestion, was higher than normal. Co-administration of taurine with toxic dose of bisphenol A could prevent the increase of serum level of ALT and AST. Liver is the first and most important organ in which BPA metabolism occurs. Consequently, the liver can be more vulnerable to low BPA doses than other organs. BPA is generally metabolized by the CYP2C cytochrome family in the liver through two pathways⁽²¹⁾.

BPA is metabolized and eliminated by combining with a glucuronide and /or a sulfate. Alternative pathway includes corrosion by hydroxylation to a catechol, then alteration to an o-quinone. The catechol-o-quinone formed is the main cause of interference in the redox cycle along with reactive oxygen species (ROS) formation. These findings were in agreement with **Muhammed et al.**⁽²¹⁾ in their previous study. Where there is increase in both ALT and AST after use BPA in rats at dose 10mg/kg/day orally for 5 weeks. The results in harmony with **Abdel Samie et al.**⁽²²⁾ in their study. Where there increases in both ALT and AST after use BPA in rats at dose 20mg/kg/day for 6 weeks by oral route were recorded. Similar results shown by **Elhamalawy et al.**⁽²³⁾ in their study in both ALT and AST after use BPA in rats at dose 50mg/kg/day for 4 weeks by oral route.

These findings were in disagreement with previous study recorded by **Kazemi et al.**⁽²⁴⁾, showed that BPA caused a significant decrease in AST serum levels in rats. However, the serum levels of ALT did not show any significant change in animals receiving BPA in comparison with control group, after using BPA in

rats at dose 5 microgram/kg/day for 2 months. This result explained by using small dose of BPA.

In the present study, there is significant statistical decrease in the mean values of ALT and AST in group IV as compared to group III. The protective effects of taurine against BPA-induced oxidative stress might be attributed to their ability of reducing and scavenging the ROS. Also, it is responsible for induction the activities of antioxidant enzyme⁽²⁵⁾.

In this study BPA caused dilation and congestion of blood sinusoids. Some hepatocytes appeared less acidophilic with pyknotic nuclei, others appeared with enlarged one. In some animals the endothelium of the central appeared detached. Hepatocytes appeared shrunken deeply stained and Von kupffer cells were prominent, while taurine induced no pathological changes in liver architecture, Hepatotoxicity is supposed to result from generating free radicals. Hence, antioxidants supplementation exert an ameliorative potential.

Similar results were obtained by **Abdel Samie et al.**⁽²²⁾ in their study. Where there were marked blood vessel congestion, cytoplasmic vacuolization and necrosis, inflammatory cellular infiltration, pyknotic nucleus after 3 weeks of BPA exposure in rats at dose 20mg/ kg/day orally. The current results were in a harmony with **Muhammed et al.**⁽²¹⁾ in their study. Where there were vascular congestion, inflammatory cell infiltration and necrotic changes of hepatocytes after BPA exposure in rats at dose 10mg/kg/day for 5 week orally.

Co-administration of taurine with toxic dose of bisphenol A (group IV) led to protection of liver from previous changes, and the liver sections appeared more or less as the control group. The previous result could be explained by, taurine has been shown to protect cells against the cytotoxic effects of inflammation associated with oxidative stress and to provide anti-inflammatory effects⁽²⁶⁾. The results in agreement with **Uzunhisarcikli and Aslanturk**⁽¹⁴⁾ in their study, where taurine used in rats at dose 100mg/kg orally. Taurine treatment significantly reversed the adverse effects of BPA on liver tissue. They noticed that the histopathological alterations in the taurine treated rats were more mild. The antioxidants caused a marked decrease in the inflammatory cells infiltration and no necrosis was visible.

CONCLUSION

It has been found that repeated exposure or consumption of substances contain bisphenol A affects liver both functionally and pathologically. Taurine has the ability to protect against hepatotoxicity and oxidative stress induced by bisphenol A.

RECOMMENDATIONS

It is advisable to restrict use of bisphenol A containing tools due to its bad effect on different body system, or using tools made of its derivatives as bisphenol F & S. Further studies should be performed on other antioxidants and evaluate its effect on bisphenol A toxicity.

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