SUB-ACUTE TOXIC EFFECTS OF BISPHENOL A ON BLOOD AND LARGE INTESTINE AND THE POSSIBLE PROTECTIVE EFFECT OF TAURINE IN ALBINO RATS

BY

**** Esam M A Ali, *Azza O Hassan, *Maha A Helal, ** Doha S Mohamed, *Marwa A HasbElnabi***

Department of Forensic Medicine and Clinical Toxicology and Department of Histology**, Faculty of Medicine, Sohag University, Egypt*

ABSTRACT

Background: Bisphenol A (BPA) is a plastic toxin widely used in manufacturing of plastic containers. It is known to produce a variety of toxic effects on body functions weight organic compound in living organisms. **Aim of the work:** This study was designed to demonstrate the sub-acute toxic effect of bisphenol A on blood and large intestine of adult male albino rats and if there is any protective role for taurine. **Material and methods:** Forty adult male albino rats were divided into four groups: Group I (Control group), Group II (Taurine only group) received Taurine orally at the dose of 100 mg /kg /day. Group III (Bisphenol only group) treated orally with bisphenol A at dose 130 mg /kg /day. Group IV (Bisphenol & Taurine group) received orally bisphenol A and Taurine at the same mentioned dose. After one month, all rats were sacrificed, and blood was collected for measurements of hematological parameters. The large intestine was preserved for histopathological examination by light microscope. **Results**: Results of the present study revealed highly statistically significant decrease (P<0.001) in the RBCs count, Hb concentration, HCT, MCV, MCH and percentage of lymphocytes and mid-cell fraction while there is statistically significant increase (P value: 0.002) in platelets count and highly statistically significant increase (P<0.001) in WBCs count in BPA only group III compared with control group I. There is non-significant change in percentage of neutrophils. BPA exposure also induced histopathological changes like inflammatory cell infiltration, decease thickness of the crypts of the colon with congested dilated blood vessels, some mucosal cells appeared degenerated others have necrotic nuclei and the smooth muscles appeared vacuolated in large intestine tissue. These toxic effects declined markedly by concomitant administration of taurine with bisphenol A. **Conclusion**: From the results of the present study, it was concluded that bisphenol A leads to many toxic effects on hematological parameters and large intestine and taurine has a potential protective role against such harmful effects.

Keywords: *Bisphenol A, Taurine, Hematological parameters, large intestine*

Corresponding author: *Dr. Azza Omar Hassan*
Email: profazza511@gmail.com

INTRODUCTION

The manufacturing of epoxy resins and polycarbonate plastic products commonly uses bisphenol A. a variety of food and beverage receptacles, including food containers and bottles of water and baby feeding are made of polycarbonate plastic materials. Metal cans used to package various sorts of food are lined with epoxy resins. As a result, many people consume food and liquids that are contaminated with BPA ***(Dixit et al., 2017).***

The large public is frequently subjected to bisphenol A via way of eating (drinking water and bottled meals) andby medical goods and techniques such as heart-lung bypass surgery, dermal exposure, kidney dialysis, toothfillings and household dusts inhalation and it has been identified in different body fluids and human tissues. Animals and people may be adversely affected by BPA in the environment ***(Chen et al., 2022; Uzunhisarcikli and Aslanturk, 2019).***

A xenoestrogen, Bisphenol A mimics natural effects of estrogen while causing negative health effects. BPA has been linked to oxidative stress in the liver, kidneys, and brain as well as disruptions in

the control of cytokines in addition to its estrogenic activities. The kidneys excrete BPA and accumulate when the glomerular filtration rate is low. Furthermore, Patients who suffer from chronic renal impairment have been found to have higher BPA plasma levels ***(Poormoosavi et al., 2018).***

Studies have demonstrated that bispnenol A has a variety of harmful consequences, including toxicity to the reproductive system and development, neurotoxicity, immunotoxicity, and it may even raise the risk of some cancers ***(Ni et al., 2022).***

It has been shown that bisphenol A is linked to mitochondrial disorders and oxidative stress. Oxidative stress causes an elevation in the reactive oxygen species release, which cause several histopathological lesions ***(Apaydin et al., 2016; Khan et al., 2016).***

By producing ROS via raising lipid peroxidation and lowering the activity of antioxidant enzymes, bisphenol A induces tissue damage in the brain, kidney, liver, and some other organs, leading to oxidative stress. ***(Bindhumol et al., 2003; Kabuto et al., 2004).***

For the study of toxicology, hemological investigations are essential. These are utilized to evaluate animal system relationships, physiological responses, and frequently measurable variables **(Ghosh et al., 2016).**

Bisphenol A induces significantly lower RBCs count and Hb level; also BPA may lower the iron concentration in the circulation and shorten the half-life of erythrocytes due to membrane changes ***(Abid and Hassan, 2017)***.

The health of the gut, which is the body's largest organ of immunity, is crucial to maintaining public health. Previous research has shown that BPA induces dysfunction of mitochondria (in vitro) in an intestinal epithelial cell model, causing cell death and intestinal barrier dysfunction ***(Zhao et al., 2019).***

Many investigations have demonstrated that the antioxidant activities of several natural and synthetic compounds protect against toxic effects of BPA. Supplementation with antioxidants may be required to minimise BPA toxicity ***(Mahmoudi et al., 2015).***

Taurine is 2 aminoethanesulfonic acid and is the most prevalent amino acid found inside cells. It is involved in several essential biological processes including intracellular calcium concentration regulation, osmoregulation, bile acid conjugation and the biological membrane's stability ***(Marcinkiewicz and Kontny 2014).***

THE AIM OF THE WORK

The aim of this study was to demonstrate the subacute toxic effect of bisphenol A on blood and large intestine of adult male albino rats and determine the possible protective role for taurine on the toxicities induced by bisphenol A.

MATERIAL AND METHODS

Chemical compounds:

1. ≥ 99% pure BPAparticles were bought from the Egyptian company Sigma Aldrich.
2. ≥ 99% pure Taurine powder was bought from the Egyptian company Sigma Aldrich.

Animals:

Forty adult male albino rats, from Sohag University Experimental Animal House, weighing 200 ± 20 gm., were utilized in this study. Animals were housed 10 rats/cage and were kept at ambient temperature in cages of polypropylene, 21± 3 °C. At the start of the treatment protocol, rats were given a one-week acclimatization period to the lab environment. Standard pellet food and water were used to feed the animals. The Sohag University Faculty of Medicine's Medical Research Ethics Committee approved the experiment, and it was conducted in accordance with its set guidelines for the use and care of laboratory animals.

The experiment's design:

The rats were randomly separated into four groups with 10 rats each classified as follows:

Group I:

Subgroup 1 (Negative control group): The rats received basal diet and distilled water.

Subgroup 2 (positive control group): each rat was given distilled water orally for one month

Group II (Taurine only group): Rats were given taurine (100 mg/kg/day) in distilled water orally for one month ***(Kalender et al., 2019).***

Group III (Bisphenol A only group): Rats were given 130 mg/kg/day of bisphenol A dissolved in distilled water solution orally for one month. For male rats, 3250 mg/kg body weight is the oral LD50 for bisphenol A.

(Michalowicz, 2014). In this investigation, rats received bisphenol A orally at a dose of 1/25 of the LD50.

Group IV (Bisphenol A & Taurine group): Rats were given bisphenol A and taurine at the same mentioned doses for one month.

During the experiment, none of the rats died.

Preparation of the dose:

- The pure Bisphenol A particles were dissolved in distilled water by using sonication bath (Ultrasonic Cleaner Set – WUS-D06 H model).In an alkaline environment (pK_a 9.9–11.3) bisphenol A dissociates and has a moderate water solubility (300 mg L^{-1} while at room temperature) ***(Rykowska and Wasiak, 2006).*** Each amount still about 24 hours at sonication bath to obtain completely dissolved bisphenol A. Each amount was prepared every 4 days at dose 2.080 gm of bisphenol A per 80 ml distilled water for 20 rats.
- The Pure Taurine powder was freshly prepared before each dose. It was completely dissolved in distilled water at dose 400mg of taurine per 20 ml distilled water.

Methods:

1- collection and preparation of samples:

At the end of experiment rats were sacrificed under light anesthesia according to guidelines of Medical Research Ethics Committee of Faculty of Medicine at Sohag University.

Venous blood samples were taken from cervical blood vessels during slaughtering for measurements of hematological parameters as soon as possible (2ml blood into tube containing EDTA anticoagulant).

Necropsy was carried out for all rats, large intestine tissues were taken for histopathological examination by light microscopy.

2- Hematological parameters:

Red blood cells (RBCs) count, hematocrit (HCT), hemoglobin (Hb), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), Platelets count, White blood cells (WBCs) count and differential WBCs count (the percentage lymphocytes, neutrophils and the mid cell fraction (MID) (monocytes, basophils, eosinophils and WBCs precursors) ***(Petani et al., 1997)*** were done by using automated hematology analyzer (CELLTacMek 6500) according to manufacturer instruction.

3- Histopathological examination:

The large intestine tissues for all rats were fixed in paraffin embedding and formalin 10%. Staining of five µm sections was done using haematoxylin and eosin ***(Feldman and Wolfe, 2014)*** then viewed under light microscope (Olympus CX 41 RF) and photographed.

Statistical Analysis:

Analyze of the results was done using statistical program for social science version 16.0 software (SPSS inc. Chicago, USA) was used to. All information was shown as mean ± SD. The analysis of variance test (ANOVA) was used for comparison between more than two groups. For comparing two groups, Tukey's test was used ***(Kim, 2014)***. Significant was defined as P value < 0.05. Tables and graphs were used to present the data.

RESULTS

Hematological Findings:

Alterations in hematological parameters have been drawn in tables from 1 to 4.

As shown in **table (1) and figure (1)**, there was a high significant statistical change (P value <0.001) in RBCs count and Hb concentration mean values among studied groups. There was a high significant statistical lowering (P value <0.001) in RBCs count and Hb concentration in group III (Bisphenol A only group) as opposed to group I (the control). Also there was highly significant statistical elevation in the RBCs count and Hb concentration in group VI (Bisphenol A & Taurine group) compared to group III (P value <0.001).

There are a high significant statistical change among the studied groups (P value <0.001) as regards HCT, MCV and MCH. **Table 2** shows that exposure to BPA (130 mg/kg B.W./day for one month) produces a highly significant decrease (P value <0.001) in HCT, MCV and MCH in male albino rats in comparison with control group. In comparison to group III HCT, MCV and MCH significantly increased in group VI (P value: 0.001, <0.001, 0.018 respectively).

Also as shown in **Table (3) and Figure (2)** there is a significant statistical change (P

value: 0.003) in platelet count mean value among studied groups. When compared to group I, platelet count was significantly elevated in group III (P value: 0.002). There was no statistically significant change in platelet count between group III from one side and group VI from the other side (p value > 0.05).

As presented in **table (4) and figure (3)**, there was a highly statistical significant difference (P value <0.001) in the mean value of WBCs count and percentage of lymphocytes and mid-cell fraction among studied groups. There was a significant statistical change in the mean value of percentage of neutrophils among studied groups (p value: 0.001).

The impact of BPA exposure (130 mg/kg/day) for one month demonstrated a high significant elevation (P value <0.001) in WBCs count while the percentage of lymphocytes and mid-cell fraction shows a high significant reduction (P value <0.001) in group III as opposed to group I. In group IV there was a high significant statistical decrease in the WBCs count and a high significantstatistical elevation in the percentage of lymphocytes (P value <0.001) and a significant statistical elevation in the percentage of mid-cell fraction (P value: 0.001) compared to group III. Nochange is observed in the percentage of neutrophils.

Histopathological Findings:

Group I& II: Light microscopic examination of section of the colon revealed normal different layers of the colon, mucosa, submucosa, musculosa and adventitia **(Figure 4).** The lining epithelium of the mucosa is formed of columnar absorptive cell and goblet cells **(Figure 5)**. The musculosa is formed of inner circular and outer longitudinal layer. Within the inner layer the sympathetic enteric plexus were observed **(Figure 6)**.

Group III: there were inflammatory cell infiltration and decease thickness of the crypts of the colon **(Figure 7)** with congested dilated blood vessels **(Figures 8&9)**. Some mucosal cells appeared degenerated others have necrotic nuclei **(Figure10)**.The smooth muscles appeared vacuolated **(Figure 11)**.

Group IV: The histological examination of colon showed improvement of most of the previous histological changes (inflammatory cell infiltration, decease thickness of the crypts of the colon with congested dilated blood vessels, some mucosal cells appeared degenerated others have necrotic nuclei and the smooth muscles appeared vacuolated in large intestine tissue) apart from few inflammatory cell infiltrations, no dilated or congested blood vessels and the height of the crypts are more or less as the control **(Figures 12 & 13)**.

Table (1): Statistical analysis of red blood cells (RBCs) count, hemoglobin (Hb) concentration among studied groups at the end of the study using ANOVA one way test and TUKEY's Test:

		Groups				ANOVA	
		Group I	**Group II**	**Group III**	**Group IV**	**F**	**P-value**
RBCs ($10^{\wedge 6}$)	**Range**	5.57-7.6	6.48-8.14	3.48-4.88	4.65-6.9	62.860	<0.001 (HS)
	Mean ±SD	6.944±0.809	7.506±0.587	3.904±0.448	5.503±0.674		
Hb (gm)	**Range**	12.7-16.6	15.3-17.8	7-9.1	10-14.4	100.189	<0.001 (HS)
	Mean ±SD	15.140±1.777	16.090±0.656	7.810±0.814	11.290±1.229		

TUKEY's Test						
Groups	**I versus II**	**I versus III**	**I versus IV**	**II versus III**	**II versus IV**	**III versus IV**
RBCs ($10^{\wedge 6}$)	0.224	<0.001(HS)	<0.001(HS)	<0.001(HS)	<0.001(HS)	<0.001(HS)
Hb (gm)	0.304	<0.001(HS)	<0.001(HS)	<0.001(HS)	<0.001(HS)	<0.001(HS)

ANOVA one way test (For comparison between more than two groups).
TUKEY's Test (For comparison between two groups).
Group I (Control group) - Group II (Taurine only group) - Group III (Bisphenol A only group) - Group IV (Bisphenol A & Taurine group) SD: standard deviation
P values (> 0.05 Non significant (NS), <0.05 Significant (S), <0.001 Highly significant (HS)

Table (2):Statistical analysis of hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) among studied groups at the end of the study using ANOVA one way test and TUKEY's Test

		Group I	Group II	Group III	Group IV	F	P-value
HCT (%)	**Range**	31.9-44.1	38.8-42.8	25.5-30.8	31-35.6	43.445	<0.001 (HS)
	Mean ±SD	39.380±4.894	41.300±1.630	27.850±2.166	33.290±1.761		
MCV (fL)	**Range**	53.4-59.1	52.5-59.9	41.7-45.8	51.2-53.6	93.147	<0.001 (HS)
	Mean ±SD	56.400±2.270	55.190±2.649	43.300±1.318	52.540±1.090		
MCH (pg)	**Range**	20-28.8	16.6-23.6	15.3-25.4	19.4-20.6	11.258	<0.001 (HS)
	Mean ±SD	23.180±3.134	20.440±2.375	16.690±3.088	20.180±0.379		

TUKEY's Test

Groups	I versus II	I versus III	I versus IV	II versus III	II versus IV	III versus IV
HCT	0.469	<0.001(HS)	<0.001(HS)	<0.001(HS)	<0.001(HS)	0.001(S)
MCV	0.512	<0.001(HS)	<0.001(HS)	<0.001(HS)	0.021(S)	<0.001(HS)
MCH	0.087	<0.001(HS)	0.052	0.010(S)	0.996	0.018(S)

ANOVA one way test (For comparison between more than two groups).
TUKEY's Test (For comparison between two groups).
Group I (Control group) - Group II (Taurine only group) - Group III (Bisphenol A only group) - Group IV (Bisphenol A & Taurine group) SD: standard deviation
P values (> 0.05 Non significant (NS), <0.05 Significant (S), <0.001 Highly significant (HS)

Table (3): Statistical analysis of platelets count among studied groups at the end of the study using ANOVA one way test and TUKEY's Test:

Groups	platelets ($10^{\wedge 3}$) count						ANOVA	
	Range			Mean	±	SD	F	P-value
Group I	395	-	572	509.600	±	66.595	5.574	0.003 (S)
Group II	453	-	752	629.200	±	118.211		
Group III	515	-	774	669.100	±	94.436		
Group IV	529	-	744	611.200	±	75.924		

TUKEY's Test

I versus II	I versus III	I versus IV	II versus III	II versus IV	III versus IV
0.028 (S)	0.002 (S)	0.077	0.761	0.971	0.493

ANOVA one way test (For comparison between more than two groups).
TUKEY's Test (For comparison between two groups).
Group I (Control group) - Group II (Taurine only group) - Group III (Bisphenol A only group) - Group IV (Bisphenol A & Taurine group) SD: standard deviation
P values (> 0.05 Non significant (NS), <0.05 Significant (S), <0.001 Highly significant (HS)

Table (4):Statistical analysis of white blood cells (WBCs) count and percentage of Lymphocytes, neutrophils and the mid-cell fraction (MID) among studied groups at the end of the study using ANOVA one way test and TUKEY's Test :

		Groups				ANOVA	
		Group I	Group II	Group III	Group IV	F	P-value
WBCs (10^3)	Range	7.35-14.46	8.02-10.55	14.38-18.85	4.57-14.57	23.044	<0.001 (HS)
	Mean ±SD	9.900±2.670	9.154±1.001	16.497±1.630	8.888±3.453		
Lymphocytes %	Range	22.3-31.9	53.7-73.9	10.5-20.2	58-64.5	212.850	<0.001 (HS)
	Mean ±SD	27.150±3.931	61.680±8.035	16.340±3.528	60.440±2.839		
Neutrophils %	Range	10.8-29.8	11.4-19	1.6-32.4	23.7-31	6.530	0.001 (S)
	Mean ±SD	17.120±7.007	15.440±3.284	21.480±11.023	27.940±3.035		
MID %	Range	11.1-16.1	9.8-11.6	6.4-11.9	9.8-13.9	15.201	<0.001 (HS)
	Mean ±SD	13.280±1.729	10.640±0.698	8.920±1.807	11.620±1.421		

TUKEY's Test

Groups	I versus II	I versus III	I versus IV	II versus III	II versus IV	III versus IV
WBCs (10^3)	0.896	<0.001(HS)	0.778	<0.001(HS)	0.994	<0.001 (HS)
Lymphocytes %	<0.001(HS)	<0.001(HS)	<0.001(HS)	<0.001(HS)	0.945	<0.001 (HS)
Neutrophils %	0.948	0.500	0.007(S)	0.223	0.001**(S)**	0.175
MID %	0.002(S)	<0.001(HS)	0.076	0.062	0.459	0.001**(S)**

ANOVA one way test (For comparison between more than two groups).
TUKEY's Test (For comparison between two groups).
Group I (Control group) - Group II (Taurine only group) - Group III (Bisphenol A only group) - Group IV (Bisphenol A & Taurine group) SD: standard deviation
P values :> 0.05 Non significant (NS), <0.05 Significant (S), <0.001 Highly significant (HS)

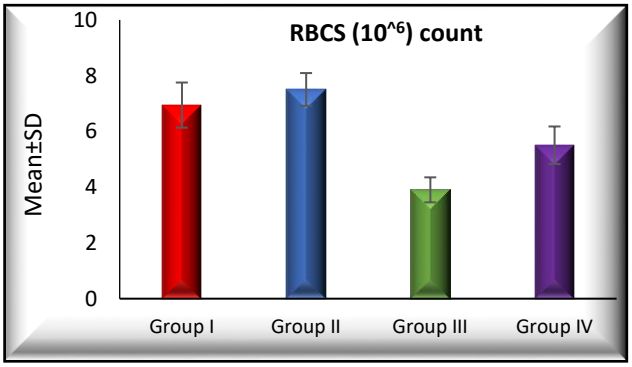

Figure (1): *Bar chart showing RBCs count in the studied groups (group I, group II, group III and group IV).*

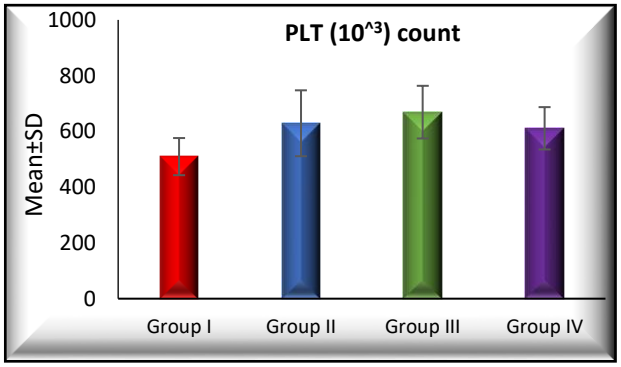

Figure (2): *Bar chart showing platelets count in the studied groups (group I, group II, group III and group IV).*

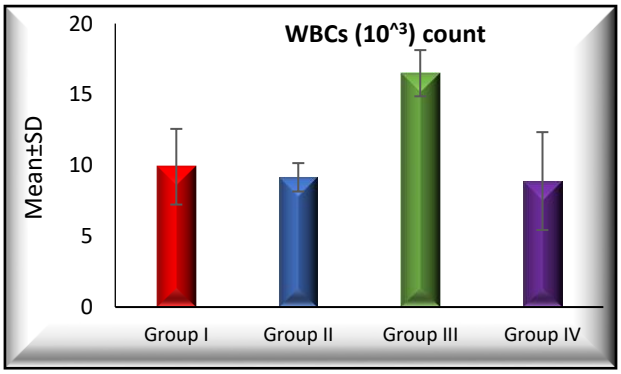

Figure (3): *Bar chart showing WBCs count in the studied groups (group I, group II, group III and group IV).*

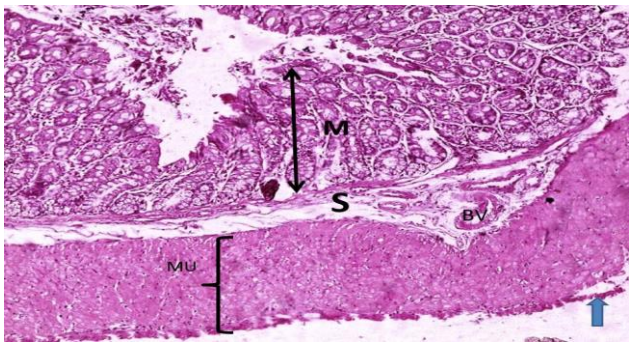

Figure (4): *A photomicrograph of a section from large intestine of control group rat* ***(Group I& II)*** *shows the different layers , Mucosa(M), submucosa (S), musculosa (MU) and adventitia (thick arrow)* ***(H&E x100).***

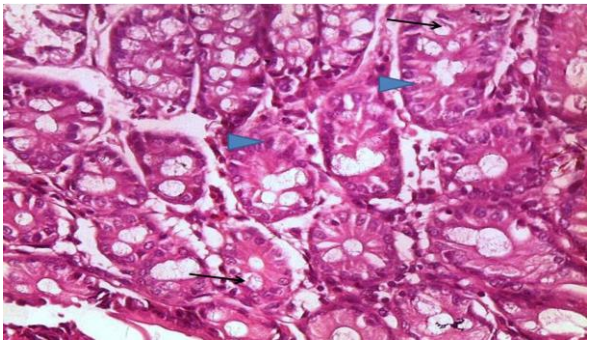

Figure (5): *A photomicrograph of a section from large intestine of control group rat* ***(Group I& II)*** *shows a magnified image of mucosa of the previous section shows the absorptive columnar cells (arrow heads) and goblet cells (arrows)* ***(H&E x 400)***.

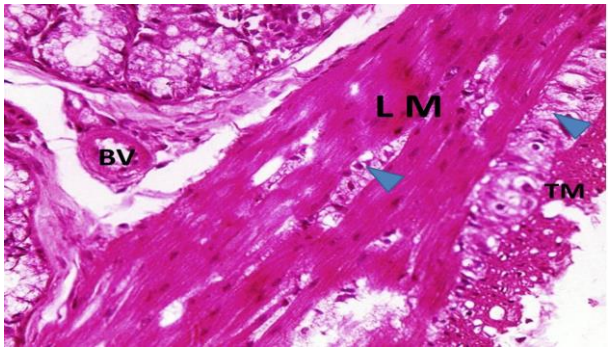

Figure (6)*: A photomicrograph of a section from large intestine of control group rat* ***(Group I& II)*** *shows magnified image of muscles of the previous section shows the longitudinally cut circular smooth muscles* ***(LM)*** *and transversally cut smooth muscles* ***(TM)****. Note the blood vessel* ***(BV)*** *and sympathetic ganglion (arrow heads)* ***(H&Ex400)***.

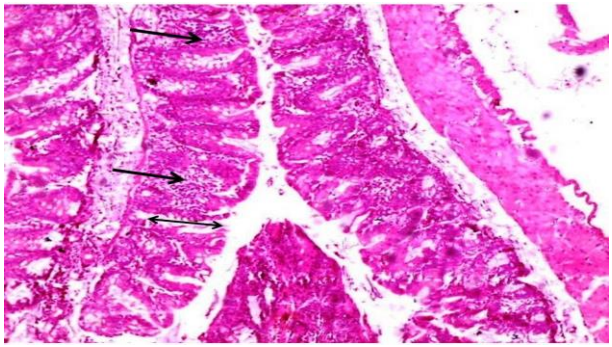

Figure (7): *A photomicrograph of a section from large intestine of bisphenol A only group rat* ***(Group III)*** *shows inflammatory cell infiltration (arrows) and decease thickness of the crypts of the colon (double head arrow)* ***(H&Ex 100).***

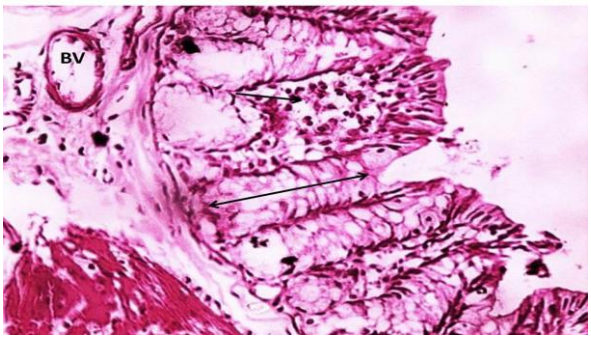

Figure (8)*: A photomicrograph of a section from large intestine of bisphenol A only group rat* ***(Group III)*** *shows magnified image of mucosa of the previous section shows inflammatory cell infiltration (arrows) and decease thickness of the crypts of the colon (double head arrow) and dilated blood vessels (BV)* ***(H&Ex400).***

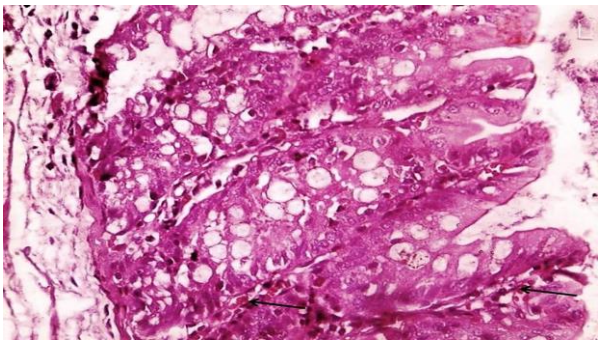

Figure (9)*: A photomicrograph of a section from large intestine of bisphenol A only group rat* ***(Group III)*** *shows magnified image of mucosa of the colon shows congested blood vessels (arrows)* ***(H&E x400)***.

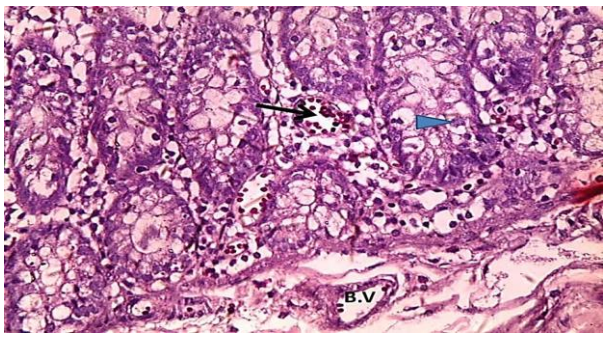

Figure (10): *A photomicrograph of a section from large intestine of bisphenol A only group rat* ***(Group III)*** *shows magnified image of mucosa of the colon shows congested (arrows) dilated blood vessels (BV) with degeneration of the epithelial lining (arrow head)* ***(H&E x400).***

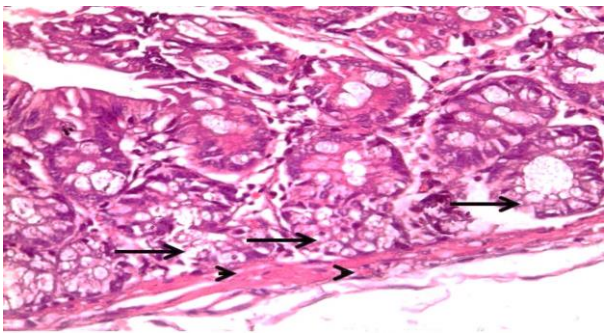

Figure (11) *: A photomicrograph of a section from large intestine of bisphenol A only group rat* ***(Group III)*** *show magnified image of mucosa of the section shows destroyed degenerated crypts with pyknotic nuclei of its cells (arrows) the smooth muscles of muscularis mucosa is vacuolated (arrow head)* ***(H&Ex400).***

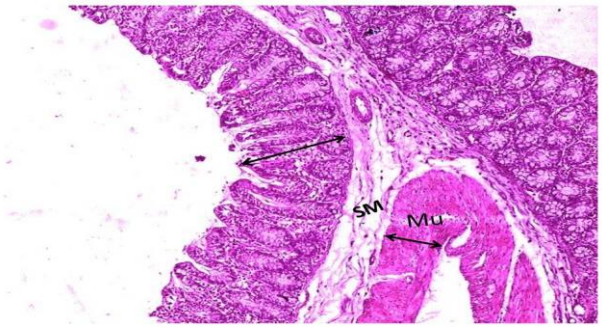

Figure (12): *A photomicrograph of a section from large intestine ofbisphenol A & taurine group rat* ***(Group IV)*** *shows less inflammatory cell infiltration compared to the previous group with restoration of the crypt thickness (double head arrow). Note the submucosa (SM) and musculosa* ***(H&Ex 100).***

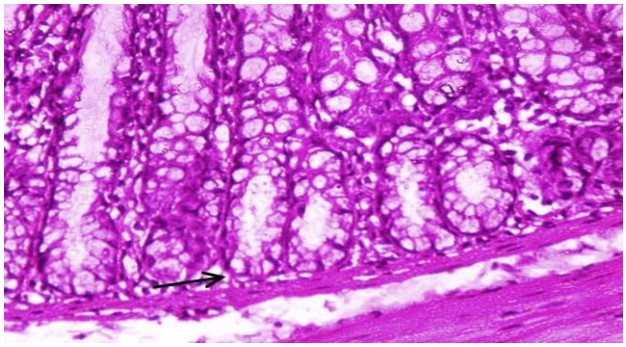

Fig (13)*: A photomicrograph of a section from large intestine of bisphenol A & taurine group rat* ***(Group IV)*** *shows a magnified image of the mucosa of the section shows less inflammatory cell infiltration (arrow) compared with previous group* ***(H&Ex400).***

DISCUSSION

Bisphenol A is a prevalent endocrine-disrupting substance, and its estrogenic action was reported in the initial stages of its use (1960s). In the context of its main usage and adverse impacts on health of humans, especially on reproduction, BPA usage was controlled. The United States Environmental Protection Agency has determined a dose as a reference of 50µg/kg/day. In addition, the European Food Safety Authority has determined a temporary daily acceptable consumption of 4µg/kg/day ***(Gore et al., 2015).***

It should be noted that BPA was prohibited from baby bottles in many countries. Since worries about human health, regulations restricting BPA use have increased, the utilization of the remaining bisphenols as BPA substitutes has become more widespread. In recent years, studies on BPA have increased, showing that BPA has other endocrine disturbance aspects together with its estrogenic activity ***(Kim and Park, 2019).***

BPA exposure in humans is unavoidable because these chemicals are widely used. Subsequently, nearly all examined serum samples taken from individuals in developed countries contain BPA. It can be found in human serum, urine, amniotic fluid, samples of placental tissue, and blood drawn from the umbilical cord. BPA exposure can occur orally, topically and even through inhalation. ***(Bosch et al, 2016; Ni et al., 2022)***.

Oxidative toxicity has been demonstrated by several researches after exposure to BPA in mice andrats ***(Gong and Han, 2006).***

Antioxidants are crucial for preventing BPA's oxidative stress ***(Amjad et al., 2020).*** Because it can remove reactive oxygen species, taurine has been classified as an antioxidant that prevents lipid peroxidation ***(Agha et al.***

2014). Additionally, it performs important physiological functions like xenobiotic conjugation, mitochondrial and cytoplasmic calcium homeostasis regulation, and osmoregulation ***(Huxtable 1992)***.

It has been found that Taurine is clinically effective against a variety of pollutants where cellular damage is caused by reactive oxygen species ***(Issabeagloo et al., 2011).***

There was a highly significant statistical decrease in RBCs count, Hb concentration, HCT, MCV and MCH in group III as opposed to groupI.

These findings are in line with ***Abid and Hassan, (2017)*** who demonstrated that rats administered bisphenol A at 250 mg/kg orally for 30 days leads to a significant reduction in RBCs count and Hb concentrations as opposed to control group. The bisphenol A lowers the blood iron level or lead to a reduction in RBCs half-life and their degradation due to changes in cell membrane permeability that increase the fragility and hemolysis susceptibility of red blood cells.

Also, ***Hameed et al. (2020)*** revealed significant reduction in RBCs, Hb level, HCT and MCV in the BPA-treated wistar rats at doses of 10 and 25 mg/kg orally of twelve weeks duration in comparison with control groups. Also, they found significant decrease in MCH percentage value in rats received BPA orally at 25 mg/kg for 6 weeks and rats received BPA orally at 25 mg/kg for twelve weeks compared to control groups. The lowering in rats hematological parameters may be caused by BPA-induced hemolysis and shrinkage of RBCs, resulting in a significant reduction in hematocrit value which induces anaemia.

These results were consistent with **Afzal et al. (2021),** who revealed that the oral bisphenol A consumption for 28 days at 10, 50 and 100 mg/kg/day causes significant lowering in the level of hemoglobin, HCT and red blood cells in treated rabbits in comparison with control group.

The fall in RBC count may be caused by a decrease in the formation rate and an increase in the rate of destruction of RBCs ***(Hameed et al., 2020).***

Additionally, ***Ahmed et al. (2015)*** foundthat oral administration of bisphenol A to rats at dose 150 mg/kg of bisphenol A for 70 days leads to significant lowering in RBCs count, Hb level and HCT as opposed to control group. Meanwhile, they found no significant change regarding MCV between BPA received group and the control group. Bisphenol A exposure leads to normocytic normochromic anemia.

The results of ***Geroge et al. (2009)*** revealed a significant reduction in erythrocyte count in rats received BPA at 400 mg/kg and hemoglobin in rats received BPA at 600 mg/kg orally for 21 days compared to control groups and explained this acute anemia because BPA enter into erythrocytes and is either oxidized or denature hemoglobin. Thus protein inadequacy inhibit erythrocyte production requirement. Meanwhile, they found that MCV and HCT were significantly elevated in 400 and 600 mg/kg treated groups as opposed to control.

Karnam et al. (2015) revealed significant reduction of the Hb level and HCT in rats after oral consumption for 28 days of BPA at 200, and 600 mg/kg as opposed to control group. While significant lowering in total erythrocyte count was noticed in rats received BPA for 28 days at of 600 mg / kg orally. The simultaneous reduction in erythrocyte count and an increase in BPA dose suggested that the BPA may have toxic bone marrow inhibitory effects which would reduce erythropoiesis and result in normocytic hypochromic anaemia. Meanwhile, they found no significant differences in MCV and MCH**.**

Baralic et al. (2020) reported that administration of BPA at dose of 25 mg/kg orally for 28 days lead to significant increase of RBCs count, hemoglobin concentration and HCT in treated group as opposed to the control group with no significant change in MCV and MCH in treated group as opposed to control. Noticed increase in erythrocyte count, hemoglobin concentration and HCT may be due to a reduction in water usage (possible dehydration).

The results of this study revealed significant elevation in the RBCs count, Hb concentration, HCT, MCV and MCH in bisphenol A & taurine group (Group IV)

compared to bisphenol A only group (Group III).

Zahran et al. (2019) found that taurine improve hematological parameters in albino mice that administrated carbon tetrachloride (CCl4) as there was a significant elevation in RBCs and Hb, HCT values in taurine treated group compared to CCl4 group.

Also, ***Ghosh et al. (2016)*** found that the toxicity caused by lambda-cyhalothrin on the haematological parameters of rats is significantly reduced by pretreatment with taurine. Taurine's haematoprotective mechanism may be attributed to its anti-anemic properties which strongly support haemopoiesis.

The current work showed a significant statistical increase of Platelet count in the bisphenol A only group as opposed to the control group. There was no significant change in platelet count in bisphenol A & taurine group (Group IV) compared to bisphenol A only group (Group III).

The present study findings are in line with ***Hameed et al., (2020)*** who reported a significant elevation of platelet count in the wistar rats received BPA at 25 mg/kg orally for 12 weeks as opposed to control group.

Alabi et al. (2021) reported significant increasein platelets count after consumption of 0.3 mL of BPA at 1 and 5mg/kg doses for 35 day orally in albino mice. The body's immune system, wound healing, and the various stages of blood coagulation all benefit from platelet function. An elevation of platelets could demonstrate that BPA is having harmful impacts on the immune system.

As shown in this study, The exposure effect of BPA (130 mg/kg /day) for one month demonstrated a high significant increase in WBCs count while the percentage lymphocytes and mid-cell fraction shows a high significant lowering in BPA only group as opposed to the control group. No difference was noticed in the percentage of neutrophils.

This coincides with the results of ***Abid and Hassan (2017)*** who revealed that there is a significant elevation of WBCs count and a significant lowering of the percentage of lymphocytes in BPA (250 mg/kg orally for 30 days) treated rats as opposed to the control group. Increases in WBCs count following BPA exposure can be explained by BPA's role in induction of inflammatory conditions and possibly as a result of immune system stimulation and stress caused by BPA. Meanwhile, they found significant elevation of the percentage of neutrophils and non-significant changes in percentage of monocyte, basophil and eosinophil in BPA treated rats as opposed to control group.

These findings go in harmony with ***Alabi et al. (2021)*** who reported significant elevationin WBCs count after oral BPA consumption of 0.3 mL (0.5, 1.0, 2.0, and 5.0 mg/kg) for 35 day. An increase in blood WBC levels signifies an elevation in defensive power of an organism against infection risks and it is essential for general and specific immunity. Increased WBC concentrations may potentially indicate immune system activation as a result of BPA damage.

This is in line with the study of ***Hameed et al. (2020)*** who revealed that WBC count was significantly increase in rats received orally BPA at 25 mg/kg for six weeks and in the rats received orally BPA at 10 and 25 mg/kg for twelve weeks as opposed to the control group. Also, they found significant statistical lowering in percentage lymphocytes, monocytes and eosinophils in the oral BPA-treated wistar rats at 10 and 25 mg/kg for twelve weeks as compared to control group.

Furthermore, ***Karnamet al. (2015)*** reported significant lymphocytopenia in treated rats after oral administration ofBPA for 28 days at doses 200, and 600 mg/kgcompared to the control group. Repeated doses of BPA may cause lymphocytopenia, which may have an immunosuppressive impact**.**

Afzal et al. (2021) found that the oral BPA administration for 28 days at doses of 10, 50 and 100 mg/kg/day cause significant increase in WBCs count in treated rabbits. meanwhile, they found that neutrophil percentage significantly elevated in treated rabbits as opposed to control group.

Opposite results were observed by ***Geroge et al. (2009)*** who demonstrated that WBCs count was significantly reduced in rats treated

with BPA at 600 mg/kg orally for 21 days when compared with control groups.

Karnamet al. (2015) noticed that administration of BPA at 200 and 600 mg/kg orally for 28 days in rats causes significant reduction in the WBCs count and percent lymphocyte and significant increase of percent neutrophil of treated animals as compared to control group. There were no significant changes on percentage eosinophil, monocyte and basophil in rats received BPA when compared with control group.

Also, ***Ahmed et al. (2015)*** reportedthat treatment of bisphenol A at dose 150 mg/kg orally for 70 days in rats lead to no significant difference in WBCs count as compared with control.

The results of the this research demonstrated that combined taurine administration led to a high significant statistical lowering in the WBCs count and a high significant and significant statistical elevation in the percentage of lymphocytes and mid-cell fraction in comparison to BPA only group.

These findings agree with the study of ***Pasantes-Morales et al. (1984)*** who revealed that lymphocytes were protected by taurine.

Taurine functions as an antioxidant preventing oxidative stress in cells in the immune system. As a result, taurine's key purpose is cytoprotection and the maintenance of homeostasis in cells involved in inflammation/oxidative stress ***(Marcinkiwicz and Kontny, 2014).***

Taurine's anti-inflammatory efficacy could be linked to its function as antioxidant in neutralising hypochlorous acids, that are reactive compounds in both monocytes and mammalian neutrophils formed via the myeloperoxidase pathway, by producing taurine chloramine, a less harmful and more stable chemical. Taurine chloramine is produced at the inflammation site and regulates cytokines expression and release like IL-6, IL-8, nitric oxide and TNF-α ***(Vahdat et al., 2021)***.

The present study revealed large intestine histopathological alterations including inflammatory cell infiltration, decease thickness of the crypts of the colon with congested dilated blood vessels. Also, some mucosal cells appeared degenerated others have necrotic nuclei and the smooth muscles appeared vacuolated.

Apaydinet al. (2018) reported that there was edema and necrosis of villous of small intestine after exposure to BPA at dose 130mg /kg/day orally for 28 day.

Akram et al., (2021) found that fish subjected to BPA various concentrations showed intestinal histopathological changes include sporadic haemorrhages, inflammatory reaction, necrosis, congestion and extensive enterocyte vacuolation.

The histologic alterations might be explained by free radical and reactive oxygen species production by bisphenol metabolism. Such radicals impair cell and organelle membrane permeability ***(Lin et al., 2013)***.

BPA consumed orally comes into direct touch with the gastrointestinal mucosal cells; as a result, it is possible to have harmful impacts on the gastrointestinal tract and accelerate the change of the gut cells. In fact, mice's barrier function was disturbed by BPA treatment, which also caused intestinal toxicity ***(Nair et al., 2022).***

It could be linked to BPA's oxidative impacts on cells. Because many studies have found that BPA causes oxidative damage to cells ***(Mahmoudi et al., 2015).***

In the current study the ameliorative effect of taurine was confirmed by improvement of most of the previous histological changes.

Uzunhisarcikli and Aslanturk (2019) foundthat the antioxidant supplementation of taurine induced a significant reduction in the infiltration of inflammatory cells with no sign of necrosis in the tissues of liver of taurine plus BPA administrated rats.

Kalender et al., (2019) revealed that taurine supplementation inhibited BPA-induced necrosis in testis tissues.

Taurine's intracellular calcium-mobilizing and membrane stabilising activities may help protect against necrosis ***(Marcinkiewicz and Kontny, 2014).***

Additionally, numerous researches shown by reducing oxidative stress, taurine attenuated necrosis ***(Erdem et al. 2000).***

Taurine shows in mammalian cells a variety of therapeutic effects, including antioxidant activity ***(Wang et al., 2015).***

In biological system, taurine's therapeutic effect as an antioxidant has been linked to its power to keep biomembranes stable as well as remove ROS in animals ***(Apaydin et al., 2019).***

Taurine is believed to strengthen the antioxidant defence system in the cell, keep biomembranes stable and minimise in vivo lipid peroxidation, hence avoiding apoptosis and necrotic cell death ***(Abdel-Moneim et al., 2015).***

CONCLUSION

The findings that resulted from this study confirmed that BPA has subacute harmful effects on blood and large intestine. Also, this study revealed the potential full protective role of taurine in decreasing the deleterious effects following bisphenol A exposure.

RECOMMENDATIONS

Bisphenol A utilization should be limited in various plasticizers as well as other industries and avoid improper plastic containers handling in order to decrease the health hazards arising from BPA exposure. It is recommended that further investigations in this regard focus on measurement of oxidative stress parameters and antioxidant effects of taurine.

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دراسة التأثيرات السمية تحت الحادة لمادة البيسفينول أ علي الدم والأمعاء الغليظة والتأثيرالوقائي المحتمل لمادة التورين في ذكور الجرذان البيضاء البالغة

عصام محمد على ، عزة عمر حسن ، ضحى محمد، مها هلال، مروة حسب النبى

الملخص العربى

البيسفينول أ هومادة سامة تستخدم على نطاق واسع في صناعة الحاويات البلاستيكية.
التورين هومادة كيميائية طبيعية في أنسجة الحيوانات وتشارك في تخليق الصفراء.
الهدف: تهدف هذة الدراسة الى إثبات تأثير التسمم تحت الحاد للبيسفينول أ على الدم والأمعاء الغليظة لذكورالجرذان البيضاء والدورالوقائي المحتمل للتوراين على هذه السميات التي يسببها بيسفينول أ.
طريقة البحث: تم توزيع أربعين من ذكور الجرذان البيضاء على أربع مجموعات بواقع 10 جرذان فى كل مجموعة: المجموعة الأولى (المجموعة الضابطة) ، المجموعة الثانية تم إعطائها التورين عن طريق الفم بجرعة 100 مجم / كجم / يوم. المجموعة الثالثة تلقت البيسفينول أ عن طريق الفم بجرعة 130 مجم / كجم / يوم. المجموعة الرابعة تلقت التورين والبيسفينول أ بنفس الجرعات السابقة. بعد شهر تم التضحية بجميع الحيوانات وتم جمع الدم الوريدى لقياس معلمات الدم وتم حفظ الأمعاء الغليظة لاجراء فحص الانسجة بالمجهر الضوئى.
النتائج: تسبب إعطاء البيسفينول أ عن طريق الفم في انخفاض كبير في عدد كرات الدم الحمراء وتركيز الهيموجلوبين والهيماتوكريت ومتوسط حجم الكرية وهيموجلوبين الكرية والنسبة المئوية للخلايا الليمفاوية وجزء الخلية المتوسطة وارتفاع كبير في عدد الصفائح الدموية وعدد كرات الدم البيضاء وحدوث العديد من التغيرات النسيجية فى الأمعاء الغليظة فى صورة تسلل الخلايا الالتهابية، وانخفاض سمك خبايا القولون، وظهرت الخلايا المخاطية المتدهورة بالمقارنة مع المجموعة الضابطة. انخفضت هذه التأثيرات السامة بشكل ملحوظ بتناول التورين مع بيسفينول أ.
الاستنتاج: بناء على ذلك نستنتج ان البيسفينول أ يتسبب فى العديد من التأثيرات السامة على معلمات الدم و الأمعاء الغليظة والتورين له دور وقائي محتمل كامل لهذه التأثيرات.
التوصيات: يجب أن يكون استخدام البيسفينول أ محدودًا في الملدنات والصناعات الأخرى مع تجنب التعامل غيرالسليم مع الحاويات البلاست