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Hepatoprotective and Antioxidant Role of Resveratrol on Bisphenol A - Induced Toxicity in Rats

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Abstract

Male albino rats of Wistar strain were injected intraperitoneally with bisphenol A or/and resveratrol for 8 weeks. Serum C-reactive protein, Alpha-fetoprotein and tumor necrosis-alpha of bisphenol A-treated rats were increased significantly. Myeloperoxidase, xanthine oxidase, nitric oxide, lipid peroxidation and total oxidative status of the liver in bisphenol A - treated rats were increased significantly, which were restored to normal in resveratrol co-treated group. Endogenous antioxidant status as the activity of superoxide dismutase, catalase and glutathione peroxidase were found to be decreased significantly in the liver of the bisphenol-A treated group, which were significantly raised in resveratrol-administered groups. The non-enzymatic antioxidants as total antioxidant and thiol levels were decreased significantly as the effect of bisphenol-A that was effectively enhanced by resveratrol treatment. The liver of bisphenol-A -treated rats showed severe congestion of the hepatic tissues as well as hemorrhage was observed. The data suggested that resveratrol exerts its protective effect by modulating the extent of oxidative status and improving the enzymatic/non-enzymatic antioxidant defense system, moreover, decreases the pathological changes in animals against the liver damage caused by bisphenol-A.

Keywords: Bisphenol-A, Resveratrol, Enzymatic/Non-Enzymatic Antioxidant.

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Introduction

Bisphenol A (BPA) is a key monomer in the production of plastics. It has been shown to be hepatotoxic. Inflammation and oxidative stress are closely linked with liver fibrosis, the major contributing factor to hepatic failure. Therefore, there is impact between chronic exposure to BPA on the development of hepatic fibrosis in male rats and to determine the cross-talk between the hepatic cytokine network, oxidative stress and apoptosis [1].

Bisphenol A (BPA), 4,40-isopropy lidenediphenol, is a ubiquitous environmental endocrine-disrupting chemical. It has been used extensively in the production of polycarbonate plastics and epoxy resins that are then used in reusable drinking and baby bottles, food storage containers, innerlining of food cans, dental sealants, currency papers, toys and computer units. BPA can be released from these products in air, water and food under high temperature and acidic or basic conditions. Moreover, people are exposed to this contaminant during handling of thermal papers used in cash register receipts through dermal contact (Biedermann et al. 2010).

Thus, human exposure to BPA is unavoidable in daily life. Neonates and infants are exposed to BPA during maternal pregnancy and/or lactation through the placenta (Wan et al. 2010). Such exposure can induce deleterious effects on reproductive organ development and disturbances in metabolic, cardiovascular, immune and neuroendocrine functions as well as cancer (Rochester 2013).

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Table(1): Oxidative stress markers of rats that exposed to BPA (50 mg/kg/ b.w) or/ and resveratrol (20 mg/kg b.w).

Group	CAT (U/g)	GPx (U/g)	SOD (U/g)	Thiol (mmole/ml)
1-Control	10.35±1.25[a]	18.95±2.02[a]	23.52±2.48[a]	0.65±0.11[b]
2-BPA group	5.01±2.32[c]	10.68±1.02[c]	12.05±1.45[c]	0.24±0.02[d]
3-Resveratrol	10.74±1.58[a]	18.99±2.36[a]	23.77±2.34[a]	0.71±0.03[ab]
4- BPA +Res	7.89±1.77[b]	15.65±2.45[b]	15.94±2.07[b]	0.47±0.05[c]

Values are expressed as means ± SE; n = 10 for each treatment group.

[a] Significant different as compared to control rats and b significant different as compared to BPA group.

The liver is an essential metabolic organ responsible for keeping homeostasis all over the body. It has several major functions such as metabolism, detoxification of xenobiotics, storage of glycogen and production of bile, cholesterol and proteins. As BPA is primarily metabolized by the liver through glucuronic acid conjugation, this organ is more vulnerable to lower doses of BPA than other organs [5].

BPA induces oxidative stress and partial fat infiltration and inhibits cytochrome P450 isoforms in the liver of rats [6].

Moon et al [5] have reported that BPA may upregulate the expression of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), inducing lipid peroxidation in the liver and impairing hepatic mitochondrial function. Chronic liver injury is one of the major causes of progressive liver fibrosis, bringing about cirrhosis, liver failure and carcinoma.

Alpha-fetoprotein (α-FP) was undertaken to correlate the various types of neoplasms with the presence of these tumor markers in the tissue and serum [7].

Resveratrol (trans- 3,5,40 trihydroxystilbene) is a phenolic phytoalexin that occurs naturally in various foods, including grapes, plums, cranberries, and peanuts. Özcan et al.[8] found that the antioxidant properties of resveratrol are dependent upon the up-regulation of endogenous cellular antioxidant systems.

Resveratrol had found to prevent the hyperoxic lung injury through its anti-inflammatory and antioxidant propertie. Dihydro-resveratrol improved acute pancreatitis-associated lung injury by inhibiting pro-inflammatory response that was associated with a suppression of the nuclear factor-kappa B [9].

There has been a general consensus concerning the positive effects of resveratrol in prevention and treatment of various disease conditions due to its potent anti-inflammatory and antioxidant potentials. A lot of works are necessary before the proposal of resveratrol in the treatment of BPA. Therefore, we are currently investigating the mode of action of resveratrol with detoxifying enzymes, such as SOD, GPx, CAT, MPO and xanthine oxidase (XO), which could be implicated in liver disorders as the effect of BPA. The association between oxidative DNA damage and BPA exposure have not been studied before, so, the plasma level of 8-OHdG was determined as a marker for DNA oxidation. The goals of this study also were to examine the effects BPA without/with resveratrol exposure on lung inflammation by evaluating the role of IL-6 and IL-2. Tumor markers were evaluated as α-FP and α-TNF. Moreover, the pathological changes were investigated.

Materials and methods

Chemicals

Bisphenol A (BPA) (purity > 99%) was obtained from Sigma Chemical Company, St. Louis, Missouri, USA. Trans-Resveratrol (>98% purity) was obtained from Cayman Chemical Company (Ann Arbor, USA).

Animals and experimental design

Male albino Wistar rats of 8 weeks and weighing 150–180 g were obtained from the animal house of Faculty of Pharmacy, Zagazig University, Zagazig, Egypt. They were maintained in a polypropylene cage and provided with standard pellet diet (Valley Group Co., Egypt) and water *ad libitum* in an air-conditioned room with regular alternate cycles of 12 h light and darkness. The animals were acclimatized for 14 days prior to their use in experiments and were handled in accordance with the Ethical Committee of Faculty of Pharmacy, Zagazig University (ECAHZU). Every effort was made to minimize the number of animals used and their suffering.

Animals were randomized into four groups of 10 rats each and were treated intraperitoneally (i.p) as below for 4 weeks: control group received physiological saline (NaCl 9%; 1 mL/kg b.w.), Bisphenol-A (BPA) group received BPA (50 mg/kg/ b.w.) in physiological saline [10] .Resveratrol (Res) group was treated with 20 mg/Kg/ b.w. of resveratrol [11] at 9.00 A.M every day. Finally, BPA + resveratrol group received the same dose of BPA and followed by resveratrol at the same doses.

Blood collection

Blood samples of the fasted rats were collected from the retro-orbital venous plexus immediately with capillary tubes (Micro Hematocrit Capillaries, Mucaps, Jiangsu, China, Mainland) under the ether anesthesia. Then, the blood was centrifuged at 3000 rpm for 15 min and serum was collected for different biochemical analyses.

Cytokines and tumor biomarkers

Serum IL-2 and IL-6 were determined using Abcam's IL-2 and Abcam's IL6 rat enzyme-linked immunosorbent (ELISA) kits, respectively. The data were presented as ng/mL.

The levels of α-TNF in were quantitated using an ELISA assay (Komabiotech INC, rat α -TNF ELISA kit, USA) according to the manufacturer's instructions. Serum α-FP was determined using Enzyme Linked Fluorescent Assay (ELFA) technique (VIDAS® AFP kits, BioMerieux, France). α-FP and α–TNF were presented as IU/mL and pg/mL, respectively.

Assay of DNA damage

The levels of 8-OHDG were determined using ELISA kit according to the manufacturer's protocol (Eastbiopharm, Hangzhou, China). The absorbance was read at 450 nm.

Preparation of tissue homogenates

Prior to dissection, liver tissues was perfused with a 50 mM sodium phosphate buffer saline (pH 7.4) and 0.1 m ethylenediaminetetraacetic acid (EDTA) to remove any red blood cells and clots. The resulting supernatant was transferred into Eppendorf tubes and preserved in a deep freeze until used for various oxidative/antioxidant assays as following.

Determination of oxidative stress

MPO is a peroxidase enzyme that was determined using fluorometric assay kit. The MPO presented as nmol/min/mL. The levels of nitrite, a stable end-product of nitric oxide (NO) production, were measured based on the Griess reaction [11] and presented as μmole/g.

Determination of antioxidant enzymes

Xanthine oxidase (XO) activity was assayed and the absorbance was measured at 650 nm.

SOD activity was measured according to **Marklund and Marklund [12]**. SOD activity is expressed as nmol/g tissue. CAT activity was determined according to **Aebi [13]** and expressed as U/g tissue. GPx activity was determined as described by **Hafeman at al. [14]** and expressed in mol/g GSH consumed min/g/ wet weight tissue.

Evaluation of non-enzymatic antioxidant

Total thiols level was determined by commercial kits and results are expressed in mM/g.

Histological evaluation

For histological examination, a portion of the liver was fixed in 10% neutral buffered formalin embedded in paraffin, sectioned and stained with hematoxylin and eosin as described previously.

Statistical Analyses

Values of the biochemical assays were given as mean ± standard error (SE). Statistically significant differences between groups were determined using Analysis of Variance (ANOVA).

Results

Immunological, tumor and DND biomarkers

Fig. 1 showed the effect of resveratrol or/and BPA on IL2 and IL6 levels. Exposed the rats to BPA increased the IL2 and IL6 levels as compared to control group, respectively. However, the treatment the rats with resveratrol combined with BPA decreased the IL2 and IL6 by 70.13% and 65.30 % as compared to BPA-treated animals, respectively.

The BPA increased the levels of α-FP and α-TNF in the rat as compared to control animals while resveratrol in combination with BPA decreased their levels as compared to BPA group (Fig. 2).

The BPA increased the activities of MPO and XO by and folds as compared to control group, respectively (Fig. 3). The concurrent administration of resveratrol and BPA decreased the activity of MPO and XO as compared to nicotine group, respectively.

The serum 8-OHDG level rose approximately by 2-fold in BPA group as compared to control rats (Fig.4). However, the treatment of the rats with resveratrol before BPA had decreased the level of 8-OHDG as compared to BPA group.

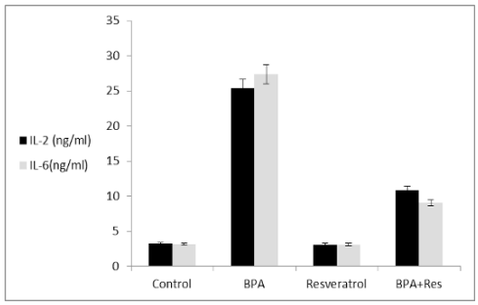


Fig. 1: Serum IL2 and IL6 levels of rats that exposed to BPA (50 mg/kg/ b.w) or/ and resveratrol (20 mg/kg b.w) for 8 weeks.
Values are expressed as means ± SE; n = 10 for each treatment group.
[a] Significant different as compared to control rats and
[b] significant different as compared to BPA group.

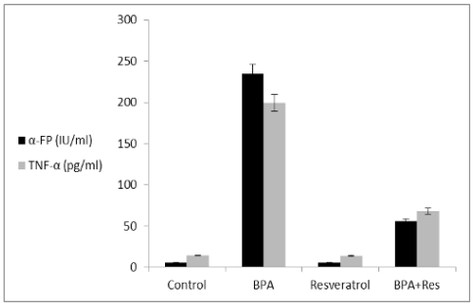


Fig. 2: Serum α-FP and TNF levels of rats that exposed to BPA (50 mg/kg/ b.w) or/ and resveratrol (20 mg/kg b.w) for 8 weeks.
Values are expressed as means ± SE; n = 10 for each treatment group.
[a] Significant different as compared to control rats and
[b] significant different as compared to BPA group.

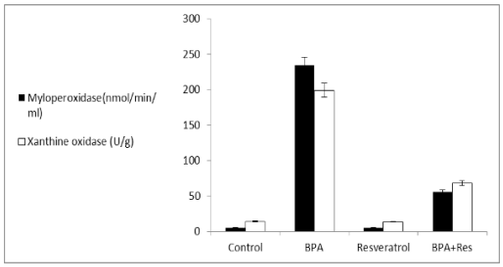


Fig. 3: Activity of MPO and XO of liver tissues of rats that exposed to BPA (50 mg/kg/ b.w) or/ and resveratrol (20 mg/kg b.w) for 8 weeks.
Values are expressed as means ± SE; n = 10 for each treatment group.
[a] Significant different as compared to control rats and
[b] significant different as compared to BPA group.

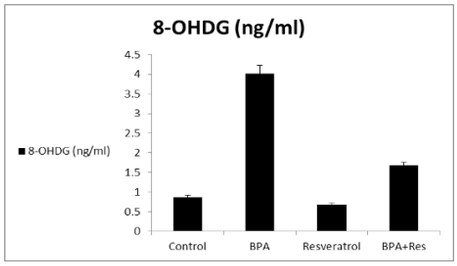


Fig. 4: Liver 8-OHDG level of rats that exposed to BPA (50 mg/kg/ b.w) or/ and resveratrol (20 mg/kg b.w) for 8 weeks.
Values are expressed as means ± SE; n = 10 for each treatment group.
[a] Significant different as compared to control rats and
[b] significant different as compared to BPA group.

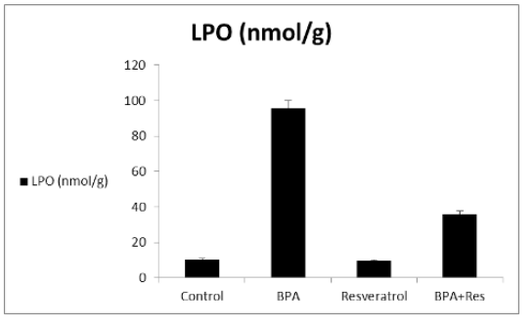


Fig. 5: Liver LPO level of rats that exposed to BPA (50 mg/kg/ b.w) or/ and resveratrol (20 mg/kg b.w) for 8 weeks.
Values are expressed as means ± SE; n = 10 for each treatment group.
[a] Significant different as compared to control rats and
[b] significant different as compared to nicotine group.

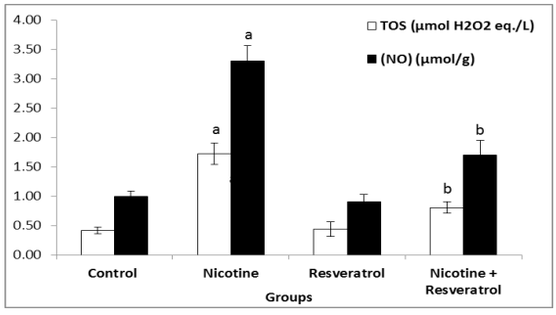


Fig. 6: TOS and NO levels of lung tissue of rats that exposed to nicotine (2.5 mg/kg/ b.w) or/ and resveratrol (20 mg/kg b.w) for 4 weeks.
Values are expressed as means ± SE; n = 10 for each treatment group
[a] Significant different as compared to control rats and
[b] significant different as compared to nicotine group.
[a] Significant different as compared to control rats and
[b] significant different as compared to BPA group.

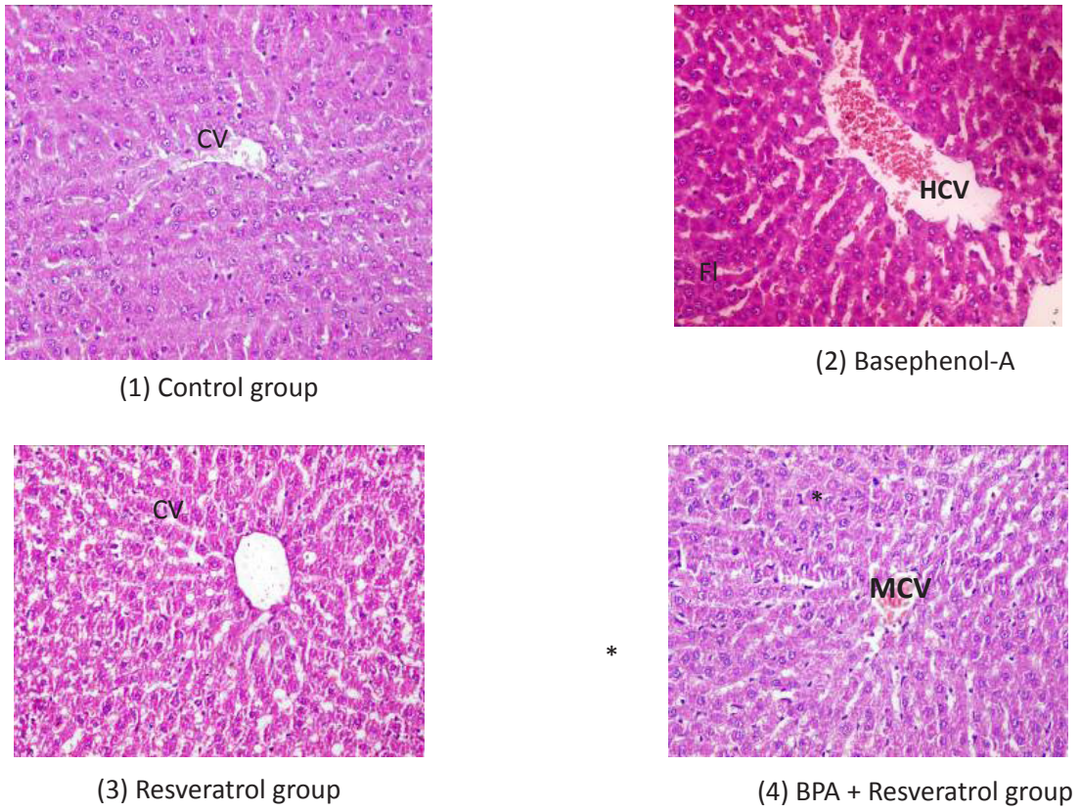


Fig. 7: Representative light micrographs of (A) liver of control rats showing normal central vein (CV) with normal hepatocytes (X400) (B) Group treated with BPA showing highly congested central vein (HCL) with appearance of focal inflammation(FI)(C) Group treated with Resveratrol showing normal hepatic structures with normal central vein (CV) (D) Group treated with combination of BPA and Res showing almost restoration of hepatic cell structures with mild congested vein (MCV) and appearance of little hydropic changes(*)(X400). All the sections have been stained with H & E.

Oxidative/antioxidant parameters

The level of LPO increased by 89.25 fold in the group of BPA as compared to control animals (Fig.5). Exposure of the rats to resveratrol and BPA had decreased the LPO by 71.51 % as compared to BPA group.

As shown in Figure 6, the effects of the resveratrol on alleviating oxidative damage caused by BPA were assessed. Rats had significant high levels of NO as compared with the control group. However, the group treated with resveratrol and nicotine was able to suppress the NO levels by 53% as compared to BPA group, respectively.

As in Table.1, the data showed that treatment with BPA caused a significant decrease in the activity of SOD of liver tissues. Administration of resveratrol (20 mg/kg b.w) did not cause any changes in the activity of SOD of liver as compared with those of control rats. In addition, a significant recovery relating to SOD was observed in response to the presence of resveratrol with BPA.

The CAT activity decreased after BPA treatment Table.1. The administration of resveratrol with BPA significantly increased the CAT activity in liver tissues as compared with BPA group.

The activity of GPx was significantly decreased in liver tissues of rats treated with BPA by 57.77 % as compared with the control group Table.1. Treatment of the animals with resveratrol did not cause any significant changes in the activity of this enzyme, while the presence of resveratrol with BPA minimized the observed alterations in examined enzyme activity induced by BPA intoxication in liver tissue.

Co-treatment of resveratrol with BPA to the rats improved the thiol level by 21.81 fold as compared with BPA group (Table.1).

Histological changes

The histological examination of control liver sections and sections of rats treated with resveratrol rats (Figs. 7 A and C) showed appearance of normal vintage hepatic lobules. Hepatocytes were polyhedral shaped, with boundaries defined pettishly. They had an acidophilic cytoplasm and central rounded nuclei with 1-2 nucleoli. Sinusoids were filled by flattened endothelial cells and Kupffer cells. Group treated with BPA showing highly congested central vein (HCL) with appearance of focal inflammation (FI) (Fig.7B). Group treated with Resveratrol showing normal hepatic structures with normal central vein (CV) (Fig.7C). Group treated with combination of BPA and Res showing almost restoration of hepatic cell structures with mild congested vein (MCV) and appearance of little hydropic changes(*) (Fig.7D). All the sections have been stained with H & E.

Discussion

Liver damage was induced by injection of BPA at a dosage of 50 mg/kg B.W. for 8 weeks. The results showed an increase in the level of oxidative and decrease in the antioxidant status in BPA-treated rats. Resveratrol treatment resulted in a decrement in the levels of all the markers of oxidative status, interleukins, α-FP and 8-OHDG while the enzymatic/ non-enzymatic antioxidant markers were significantly increased. Thus, the study shows that resveratrol offers protection against the liver damage caused by BPA.

In the present study, proinflammatory cytokines secreted from activated neutrophils, monocytes and macrophages of BPA -treated animals to remove dead cells and promote tissue repair, as α-TNF, IL-1, and IL-6 have been elevated. Our observation is in coincident with [1] who reported that BPA (50 mg/kg) administration for 8 weeks induced hepatic fibrosis in male rats. BPA mediated this deleterious effect through increasing the pro-inflammatory cytokine (IL1b) and decreasing the anti-inflammatory/anti-fibrotic cytokine (IL-10) as well as exaggerating oxidative stress through inhibition of the antioxidant enzyme activity of CAT and reduction in GSH content. All these effects enhanced hepatocyte apoptosis and hence fibrosis.

Our obtained results are greatly reinforced by Elswefy et al.[1] who indicated that oral administration of BPA-induced liver fibrosis represented by massive collagen deposition and the increase in Hyp content (fibrosis marker) in the liver tissues of rats.

α-FP contents were found to be increased by administration of BPA in the current investigation. α-FP is a tumor marker for hepatocellular carcinoma, however, wilder et al. [15] found that the elevated serum α-FP with a lung neoplasm is most likely to represent a metastasis.

In the present study, the levels of 8-OHdG increased in BPA group as compared to control animals which indicated DNA damage as the effect of BPA. 8-OHdG acts as a biomarker of oxidative stress especially to DNA, which is involved in the instigation of various diseases [16].

In the present study, MPO was found to increase in rats as the effect of BPA. During the respiratory burst, MPO utilizes H_2O_2 to produce hypochlorous acid (HClO) that reacts with proteins, unsaturated fatty acids, and any oxidizable group, to induce protein adducts and genetic mutations, and influence signaling pathways [17].

The liver is an essential metabolic organ responsible for keeping homeostasis all over the body. It has several major functions such as metabolism, detoxification of xenobiotics, storage of glycogen and production of bile, cholesterol and proteins. As BPA is primarily metabolized by the liver through glucuronic acid conjugation, this organ is more vulnerable to lower doses of BPA than other organs [5].

BPA induces oxidative stress and partial fat infiltration and inhibits cytochrome P450 isoforms in the liver of rats. Other in vivo experimental studies have shown that developmental exposure to BPA causes liver diseases, including hepatic steatosis, liver tumours and metabolic syndrome [18].

Moon et al. [5] have reported that BPA may up regulate the expression of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), inducing lipid peroxidation in the liver and impairing hepatic mitochondrial function. Chronic liver injury is one of the major causes of progressive liver fibrosis, bringing about cirrhosis, liver failure and carcinoma.

Evidences have shown that an uncontrolled inflammatory cascade and generation of reactive oxygen species (ROS) are involved in hepatic tissue remodeling and fibrosis. On these bases, hepatic fibrosis is a likely

consequence of BPA-induced liver injury. Therefore, this study aimed to explore the hepatotoxic effect of BPA after long-term exposure in male rats and to underline molecular mechanisms and the possible ameliorative effect of Res.

Excessive production of ROS in the BPA-treated group leads to LPO, and this results in oxidative stress. The elevation in the level of MDA in the liver observed in the present study may reflect the inability of the liver to eliminate ROS produced by BPA and/or inactivation of the antioxidant enzymes caused by the excess generation of ROS in the liver. Moreover, the present results demonstrated that BPA administration to rats results in elevated levels of NO in lung tissues.

LPO can be used as the index of oxidative stress and change the membrane permeability. BPA produced ROS leading to an increase in LPO in liver of rats as described before. Other previous study has been reported that oxidative stress was the mechanism responsible for toxicity developing in liver tissues due to BPA. This suggests that the increase may be due to BPA-associated excessive ROS production. Moreover, decreasing the functions of the defense system caused BPA toxicity as reported by [19].

Cells employ various antioxidant mechanisms to reduce the levels of excess ROS. In the present study, increased oxidative stress can explain the significant reduction of antioxidative enzyme activity in the liver as SOD, CAT and GPx, that suggested scavenging of free radicals from the lung tissues exposed to BPA.

The NADPH and GSH play an important role in protecting cells against ROS. GSH is regenerated from its oxidized form (GSSG) with the help of NADPH , as well as, protects the cell from oxidative damage by destroying H_2O_2 and peroxide free radicals ($OH^{\cdot}$). However, antioxidant enzymes such as SOD and CAT react against radicals such as superoxide and H_2O_2, while GPx has a scavenging effect against alkyl, alkoxy and peroxyl radicals that can be formed from oxidized membrane compounds, and uses GSH as a substrate [20]. Low levels of SOD and CAT in BPA group as compared to the control animals could increase-oxidative stress and may lead to liver damage.

The histopathological finding showed significant morphological alteration in the liver of BPA-treated rats and supported the biochemical changes. This could be due to the release of α-TNF, different types of IL and free radicals and subsequently the damage of hepatic structures and congestion of the liver.

Juan et al.[21] found that repeated consumption of trans-resveratrol at 20 mg/kg/day does not adversely affect the hematologic or biochemical parameters as well as the histopathologic examination of the organs of rats. In the present study, pretreatment with resveratrol before nicotine caused normalization of lung levels of oxidative/antioxidant parameters. It also caused significant improvement in inflammatory and tumor biomarkers. Resveratrol proved its antioxidant ability in our study by preserving TAC as well as reducing MDA levels in lungs of the nicotine + resveratrol group compared to the nicotine group.

Resveratrol has strong antioxidant activity, that may decrease oxidative stress and inhibit free radicals especially LPO products. Results from the present study are in agreement with other previous studies that reported the lower level of serum LPO products in animals fed with different concentrations of resveratrol. Resveratrol improved the antioxidant status and decreased oxidative damage to the heart and brain of rats with induced hypertension. Palsamy and Subramanian [22] showed that resveratrol effectively protects the kidneys from oxidative damage in diabetic rats. In the previous study, resveratrol decreased MDA levels and oxidative stress by increasing GSH levels. However, our data consider the first study on the effect of resveratrol against the nicotine toxicity in lung tissues.

Resveratrol is both a free radical scavenger and a potent antioxidant because of its ability to promote the activities of a variety of antioxidant enzymes. Hamza and El-Shenawy [20] found that resveratrol could function as SOD and GPx. These findings supported our results that the LPO levels were significantly lower in BPA + resveratrol group while antioxidant enzymes increased. The increase in GPx activity in liver tissues observed in this study may also be explained by the excessive production of this antioxidant, in order to scavenge the overproduction of free radicals caused by oxidative stress. The antioxidant activity of resveratrol could be also due to its ability to inhibit reductase in the ribonucleotide and cyclooxygenase 2 transcription ability in DNA polymerase activity as previously reported by Uguralp et al. (2005). The antioxidant effects of resveratrol could be due to its ability to reduce the oxidative chain reactions of ROS in competition with coenzyme Q, remove the superoxide radicals formed in the mitochondria; and prevention of LPO.

The decrease observed in 8-OHDG levels, a biomarker of oxidative DNA injury, in the BPA + resveratrol group compared to the nicotine group, also provided evidence for the antioxidant and free radical-scavenging activities of resveratrol. Our observations are in agreement with previous studies that found resveratrol has been playing an effective role in preventing oxidative DNA injury *in vivo* and *in vitro* [23].

Lai et al.[24]found that the immune function was enhanced by resveratrol treatment in immunosuppressive mice. Resveratrol involved alterations of immune cell functions and cytokine production. These results are in coincidence with the present finding that resveratrol in combination with BPA decreased the inflammatory mediators as IL2, IL6, and α-TNF as well as α-FP in liver tissues when compared to BPA-treated animals, therefore; it has anti-inflammatory and anticarcinogenic properties. In addition, Yazir et al. [25] found that the plasma levels of α-TNF in the stressed group were increased significantly compared to the control group, effects which were significantly prevented by treatment with resveratrol. This could be proved by the anti-inflammatory activity of resveratrol.

Moreover, the high concentration of NO was produced by inducible NO synthase (iNOS) in inflammation, and the prevention of the expression of iNOS might be an important anti-inflammatory mechanism [26].

In the current study, the activities of SOD, CAT, GPx, and G6PD, which changed after exposure to nicotine, were significantly increased by resveratrol treatment. Previous studies had also shown the antioxidant effects of resveratrol via elevation of the antioxidant status such as GSH and SOD [27].

In conclusion, our findings showed that the administration of BPA caused a significant elevation in LPO and significantly reduced liver antioxidant enzymes activities of male rats. The levels of biochemical mediators implicated in BPA-induced liver disorder (NO, IL-2, IL6, α-FP and α-TNF), also increase in BPA exposure animals and the development of histopathological changes that were determined in the present study. The administration of resveratrol combined with BPA ameliorated liver injury, which was associated with improving all the mentioned parameters. All these findings were confirmed by the histopathological examination, which revealed the ability of resveratrol to maintain structurally and functionally active liver tissues, which is somewhat similar to that of the control if it was administrated before the BPA.

Conflict of Interest

We declare that there are no conflicts of interest.

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