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Original Article

Curcumin and Silymarin Amelioration of the Bisphenol-A induced Hepatotoxic Effects in Male Albino Rats: A structural, Biochemical and Molecular Experimental Study

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ABSTRACT

Background: Bisphenol A [BPA] is widely used in industrial processes. It persists in environment and exerts a harmful action on human health, through endocrine-disruption. Many natural compounds are suggested to have a preventive effect on BPA-induced human health hazards.

Aim of the work: This study aimed to evaluate the effect of Silymarin/Curcumin in ameliorating the hepatotoxic effect induced in albino rats following oral administration of BPA.

Patients and Methods: Fourty adult male albino rats were included and randomly categorized into four equal groups. The control group and BPA-exposed [50 mg/kg] group. Groups 3 and 4 for rats received oral BPA [50 mg/kg] plus [100 mg/ kg] of curcumin or silymarin. Serum liver enzymes, pro-inflammatory cytokines [TNF-α & IL-1,6,8] and the oxidant/antioxidant profile were assessed in the serum. SOD, GPX and CAT levels, MDA and H2O2 were assessed. Histopathological changes of the liver, immunohistochemical detection of caspase 3 and area density of collagen fibres were also assessed.

Results: Bisphenol-A administration for 30 days was associated with a significant increase in the number of pro-inflammatory markers as interleukin 1,6,8 and tumor necrosis factor-α [TNF-α]. It also, stimulates oxidative stress with structural changes, apoptosis and fibrosis in hepatic cells. Treatment with silymarin or curcumin for 30 days lead to a reduction of pro-inflammatory mediators and significant amelioration of structural changes.

Conclusion: Silymarin/Curcumin had an ameliorative of harmful effects of BPA on the liver cells through potent anti-inflammatory, antiapoptotic and antioxidant effects.

Keywords: Bisphenol A; Liver, Oxidative stress; Hepatoprotective; Silymarin; Curcumin.

INTRODUCTION

Canned foods are widely consumed, as they contain high-quality food stuffs. However, the direct contact with packaging materials results in the contamination by some undesirable substances, such as bisphenol A [BPA] [1]. Bisphenol-A is an endocrine-disrupting compound. It is broadly used in the production of many industrial compounds. The annual consumption of BPA was approximately 8 million tons worldwide, and around 100 tons may be released within one year into the environment [2]. Several studies have revealed that BPA is widely distributed in foods, environment, and even human body fluids. Thus, different tissues and organs are affected by the toxic effects of BPA. These included liver, respiratory system, kidney, mucous membranes, immune system and the skin [3-5].

The liver is more vulnerable than other organs and tissues to BPA-induced toxic effects. BPA metabolism is achieved by the CYP2C cytochrome family, through two main metabolic pathways. The first is the elimination by conjunction with a glucuronide and/or a sulfate. The second by hydroxylation to a catechol and then alteration to an o-quinone. These is associated with oxidative stress due to interaction redox cycle and high production of reactive oxygen species [ROS] [6]. In addition, exposure to low or high doses of BPA increased oxidative stress through increased malondialdehyde [MDA] and decreasing reduced glutathione [GSH] production in the liver, which was confirmed by a previous study [7].

Different herbal products were used to alleviate the toxic hepatic effects induced by BPA. The wide spectrum of used herbs is related to the nature of used compounds, its safety, efficacy and cultural acceptance [7]. However, many natural compounds gained wide acceptance for treatment of BPA-induced harmful effects on the liver. For example, curcumin [CUR] has potential therapeutic actions on different toxic effects, exerted on different body systems [8]. In addition, silymarin is a well-known hepatoprotective compound enriched with polyphenols and flavonoids [e.g., silybin, silychristin, silybinin, and silydianin], with antioxidant therapeutic effects [9].

The potential hepatoprotective effects of CUR or silymarin against hepatoxic effects induced by BPA was not widely discussed on the molecular and structural levels. Thus, the current study was designed and aiming to assess the potential protective effects of curcumin or silymarin on the BPA- induced hepatotoxicity in albino rats by histopathological, molecular and biochemical studies.

MATERIALS AND METHODS

Chemicals: BPA [99% pure], was acquired from Sigma-Aldrich [St Louis, Missouri, USA], Curcumin [CUR] was obtained in the powder from [Sigma Chemical Company, St Louis, Missouri, USA, CAT No. 458-37-7]. Then, it was dissolved in corn oil. Silymarin [SL] was provided by [SEDICO Company, Egypt CAT No. 65666-07-1], prepared in sachets. Then, dissolved in distilled water. All were administered through oral route by intragastric tube.

Animals: Fourty adult male albino rats, weighing 120-160 g, were included. Housing was achieved in cages made of polypropylene, with 12 hours of light and dark cycles, at a temperature of 22±2°C and 10% humidity. The free access to water and standard diet pellets was permitted *ad libitum*.

Ethical approval: The study protocol was reviewed and accepted by the institutional research and ethics committee [Damietta Faculty of Medicine, Al- Azhar University, Egypt] [IRB 0001267-21-07-005]. The study also adheres to Declaration of Helsinki code of ethical reteach conduct and reporting for experimental studies. The data is available on reasonable request.

Experimental design and drug administration: Fourty adult male albino rats were left in the experimental room for 1 week prior to the study for acclimatization, then, animals were divided into four equal groups [10 rats in each group, 5 rats in a cage]. Group I [control group] received the standard rat chow diet and given normal saline [1 ml/kg body weight [BW]/day] by gastric tube for 30 days. Group 2 [BPA group], rats received BPA dissolved in corn oil and given orally in a daily dose of 50 mg/kg; Groups 3 and 4 for rats received oral, freshly-prepared BPA [50 mg/kg] plus [100 mg/kg] of silymarin or curcumin respectively for 30 days.

Blood and tissue sampling: At the 30th day of the experiment, a retro-orbital plexus was used to obtain blood samples. Samples were centrifuged at 1200g for 20 minutes, serum was separated, collected in Eppendorf tubes and kept at -20^{o} till the time of analysis.

Serum biochemical analyses: Serum concentrations of liver enzymes were examined by an automated hematology analyzer.

Determination of ROS: A piece of liver tissue (0.3 g) was homogenized in ice phosphate buffer saline using a Teflon pestle connected to a homogenizer motor (25 strokes per minute at 1000 rpm), the liver homogenate was diluted to yield 10% (w/v) then centrifuged at 13000 rpm for 30 min at 4 °C to remove cell debris and nuclei. The supernatant was used for biochemical determination of renal malondialdehyde (MDA) and H2O2.

Determination of antioxidants: Activity levels of the extra-cellular values of superoxide dismutase [SOD], glutathione peroxidase [GPx], and catalase [CAT] were measured by enzyme linked immunosorbent assays according to manufacturer's instructions [Shanghai Enzyme-linked Biotechnology Co. Ltd., Shanghai, China].

Determination of inflammatory markers: The levels of Interleukin [IL]-1β, IL-6, IL-8, and tumor necrosis factor-α [TNF-α] contents were determined using enzyme-linked immunosorbent assay kits [Shanghai Enzyme-linked Biotechnology Co. Ltd., Shanghai, China]

according to the manufacturer's instructions.

Assessment of histological and immunohisto-chemical changes: The liver specimens were fixed in 10% formalin for at least 24 hours. Then, processed and sectioned at a thickness of 5 µm, and stained by hematoxylin and eosin [Hx.&E] for the detection of histopathological [structural] changes. Masson trichrome for detection of fibrosis and immunostain for caspase-3 for detection of apoptosis. The slides were examined by light microscopy, photographed & the percentage area density of collagen fibres and caspase-3 were measured by a Raywild E5 microscope with a Raywild M-300 digital camera equipped with an image-analyzing system [Mvi-mage program v12].

Statistical analysis: The arithmetic means and standard deviation [SD] were used to represent numerical and normally distributed data. Groups were compared by one way analysis of variance [ANOVA] test with least significant differences [LSD] as a post-hoc analysis for multiple comparison. The statistical package for social science [SPSS] version 16 [SPSS Inc., Chicago, IL, USA], running on Microsoft windows personal computer, was used for all analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Liver enzymes, antioxidants and ROS: Bisphenol-A induced toxicity produced a significant increase of liver enzymes in the study than the control group. but, the concomitant administration of BPA with silymarin or curcumin produced a significant reduction of liver enzymes than BPA-exposed group. however, the liver enzymes remain significantly high when compared to the control group [Table 1].

Bisphenol-A group showed a significant reduction of SOD, GPX and CAT than the control group, confirming the role of redox system in pathogenesis of BPA-induced toxicity. The concomitant administration of BPA with silymarin or curcumin showed a significant increase of SOD, GPX and CAT levels, when compared to the BPA-exposed group. however, values remain significantly higher than the control group. Otherwise, bisphenol-A induced toxicity group showed a significant increase of MDA and hydrogen peroxide than the control group. however, curcumin or silymarin concomitantly administered with BPA was associated with a significant decrease of these levels, when compared to BPA-exposed group. however, it was significantly increased than the control group [Table 2].

Pro-inflammatory and apoptotic cytokines: Values of IL-1β, IL-6, IL-8 and TNF-α in the BPA group were markedly higher than the control group. these cytokines were significantly reduced in the groups treated with silymarin or curcumin than the BPA only group [Table 3].

The morphometric measurement of the liver sections revealed a significant increase of the collagen content and the hepatic pro-apoptotic protein caspase-3 levels in the BPA-intoxicated group than the control group. These levels were significantly decreased in groups treated with silymarin or curcumin than the BPA only group [Table 4].

Table [1]: Assay of serum liver enzymes levels in the different studied groups

	Control	BPA	BPA +SIL	BPA +CUR
ALT [U/L]	30.8±7.2	82.63 ± 4.24*	67.71 ± 3.27#	60.4±9.21#
AST [U/L]	52.26±6.34	95.64±7.26*	68±7.62#	65.32±5.18#
ALP [mg/dl]	350.64±40.67	615.74±54.43*	432±47.25#	419±36.41#

ALT: Alanine transaminase; AST: Aspartate transaminase; ALP: alkaline phosphatase; BPA: bisphenol A; SIL: Silymarin; CUR: Curcumin. * Significant differences between the BPA and control groups; # significant differences between BPA plus SIL or CUR-treated groups than BPA group.

Table [2]: Assay of oxidative/antioxidative stress parameters different groups

	Control	BPA	BPA +SIL	BPA +CUR
SOD [ng/ml]	7.06±0.37	3.31±0.43*	5.13±0.42#	4.74±0.61#
GPX [ng/ml]	6.82±0.42	2.81±0.27*	3.84±0.24#	4.06±0.31#
CAT [ng/ml]	154.64±8.3	82.36±4.91*	98.34±14.36#	127.9±8.51#
MDA [ng/ml wet tissue]	76.06 ± 3.49	298.34 ± 11.24*	114.61 ± 11.24#	108.57± 11.24#
H2O2 [ng/ml wet tissue]	1.42 ± 0.35	4.26 ± 0.74*	2.78 ± 0.34#	2.38 ± 0.18#

SOD: Superoxide dismutase; GPx: glutathione peroxidase; CAT: catalase; MDA; malondialdehyde; H2O2: hydrogen peroxide. * Significant differences between the BPA and the control groups; # significant differences between BPA plus SIL or CUR-treated groups than the BPA group.

Table [3]: Assay of serum inflammatory markers levels in the different studied groups

	Control	BPA	BPA +SIL	BPA +CUR
IL-1β [pg/ml]	91.06±15.27	217.31±21.83*	145.57±17.68#	**138.31±13.81#**
IL-6 [pg/ml]	1.51±0.38	2.74±0.51*	1.81±0.41#	**1.76±0.22#**
IL-8 [pg/ml]	104.64±9.3	52.36±7.91*	78.34±12.46#	**72.9±9.53#**
TNF-α [ng/l]	112.14 ± 3.74	236.57 ± 9.57*	145.39 ± 7.41#	**139.72± 10.44#**

IL-1β: Interleukin-1beta; IL-6: interleukin-6; IL-8: interleukin-8; TNFα: Tumor Necrosis Factor Alpha; * significant differences between the BPA than the control group; # significant differences between BPA plus SIL or CUR-treated groups than the BPA group.

Table [4]: Assessment of Liver fibrosis and apoptosis markers in the different studied groups

	Control	BPA	BPA +SIL	BPA +CUR
Collagen [µm]^2	1.36±0.27	3.57±0.83*	2..57±0.42#	**2.31±0.74#**
Caspase-3 [µm]^2	0.82±0.32	2.81±0.27*	1.21±0.31#	**1.16±0.54#**

* Significant differences between the BPA and the control group; # significant differences between BPA plus SIL or CUR-treated groups than the BPA group.

Histopathological results

Hematoxylin and Eosin-stained sections results: The hepatic sections from the control group revealed normal hepatic structure in the form of presence of central vein with radiating hepatocyte cords separated by the blood sinusoids. The hepatocytes had centrally located vesicular nucleus with acidophilic cytoplasm. The portal triad had normal appearance and contain a large venule, a hepatic arteriole and bile ductule. In the BPA-treated group, hepatocytes revealed different levels of destruction with vacuolated cytoplasm, deeply stained shrunken nuclei and dilated congested blood sinusoids with many Kupffer cells. The portal area had marked cellular infiltration, congestion of the bile duct and hepatic arteriole. The use of silymarin or curcumin showed restoration of normal shape of most hepatocytes. There were a less dilated congested sinusoids with fewer kuppfer cells. Nearly normal portal triad, portal venule, a hepatic arteriole and a bile ductule was observed, with low cellular infiltrations [Figures 1& 2].

Masson trichrome stained sections: The collagen deposition in the liver showed as significant increase [$p < 0.005$] in BPA-induced hepatotoxic rats compared to the control, whereas it significantly decreased in BPA + Sily/CUR groups in comparison to the BPA group with no significant difference between them [Figure 3].

Immunohistochemical assessment of caspase-3: Liver sections of BPA-exposed group showed marked deposition of caspase 3 than the control group. the use of curcumin or silymarin reduced the deposition of caspase-3 when compared to BPA-exposed groups. However, the difference was statistically non-significant [Figure 4].

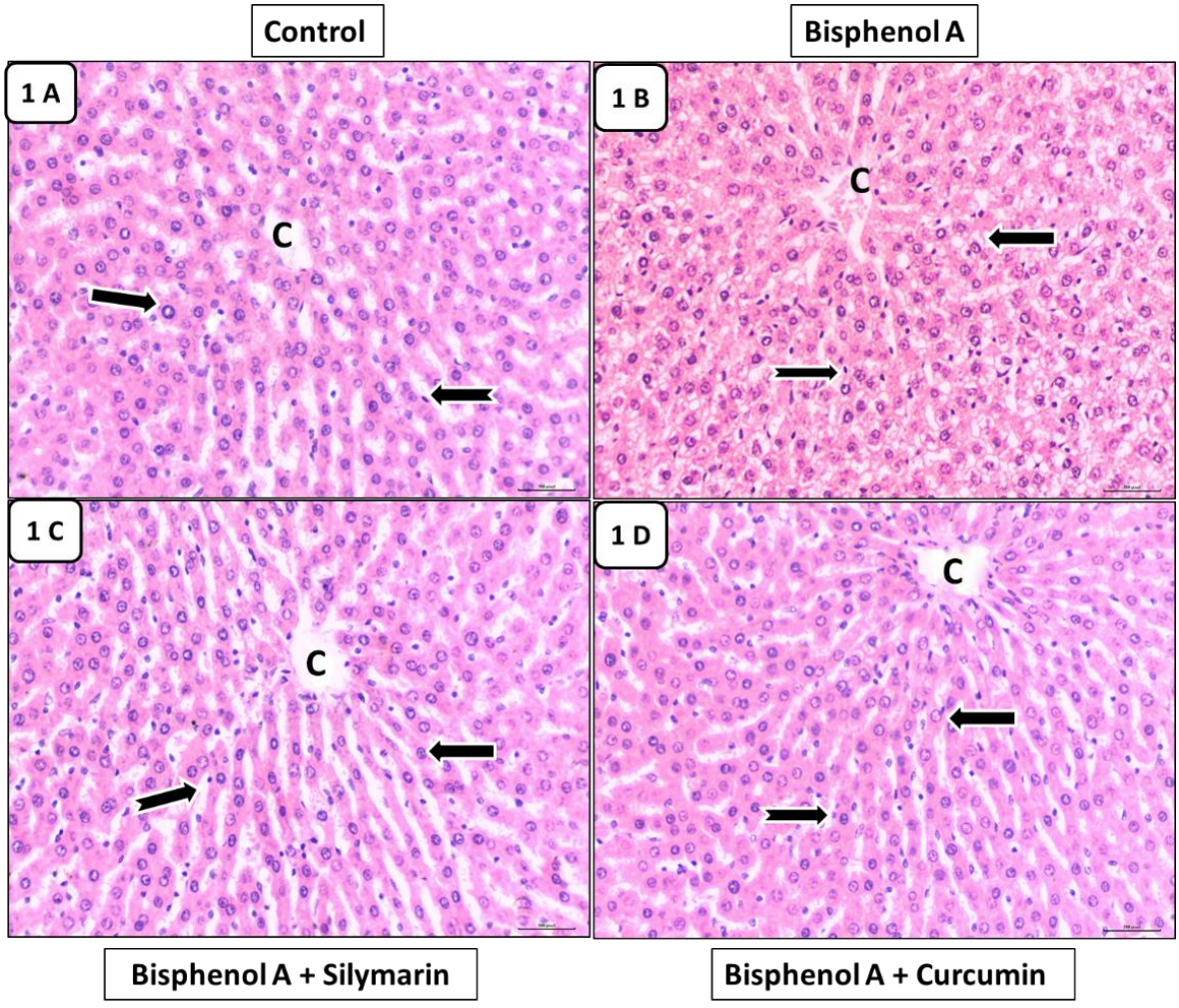

Figure [1]. [A]: The liver sections of the control group, showed normal hepatic structure in the form of presence of central vein [C] with radiating cords of hepatocytes separated by blood sinusoids [notched thick arrow], the hepatocytes showed centrally located vesicular nucleus with acidophilic cytoplasm [thick arrow]. [B]: the liver of the BPA exposed group showed; the hepatocytes appear destructed with vacuolated cytoplasm and deeply stained shrunken nuclei [thick arrow] and dilated congested blood sinusoids with many Kupffer cells [notched thick arrow]. [C, D]: the liver sections of BPA + Sily/CUR groups respectively showed; Most of the hepatocytes restore their normal shape [thick arrow], less dilated and no or minimally congested blood sinusoids with less kuppfer cells [notched thick arrow]. A: control group; B: Bisphenol A group; C: Bisphenol A + Silymarin group; and D: Bisphenol A + Curcumin group. [Hx.&E. X400] Scale bars, 200 pixel.

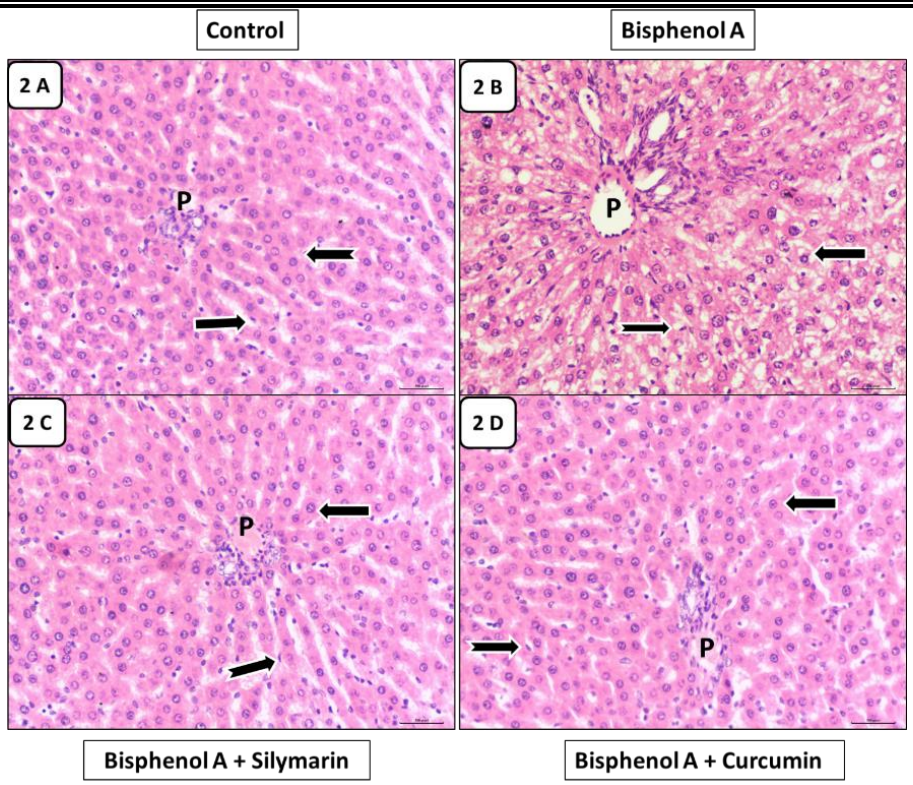

Figure [2]: [A]: The liver sections of the control group, showed the portal triad [P] was of normal appearance containing a large portal venule, a hepatic arteriole and bile ductile. [B]: In the BPA exposed group; the hepatocytes appear destructed with vacuolated cytoplasm and deeply stained shrunken nuclei [thick arrow] and dilated congested blood sinusoids with many Kupffer cells [notched thick arrow], the portal area [P] showed marked cellular infiltration, congested bile duct and hepatic arteriole. [C,D] BPA + Sily/CUR groups respectively; Most of the hepatocytes [thick arrow] restore their normal shape, less dilated and congested blood sinusoids with less kuppfer cells [thick notched arrow], almost normal portal triad [P]: portal venule, a hepatic arteriole and a bile ductule with few cellular infiltrations can be observed A: control group; B: Bisphenol A group; C: Bisphenol A + Silymarin group; and D: Bisphenol A + Curcumin group. [Hx.&E. X400] Scale bars, 200 pixel.

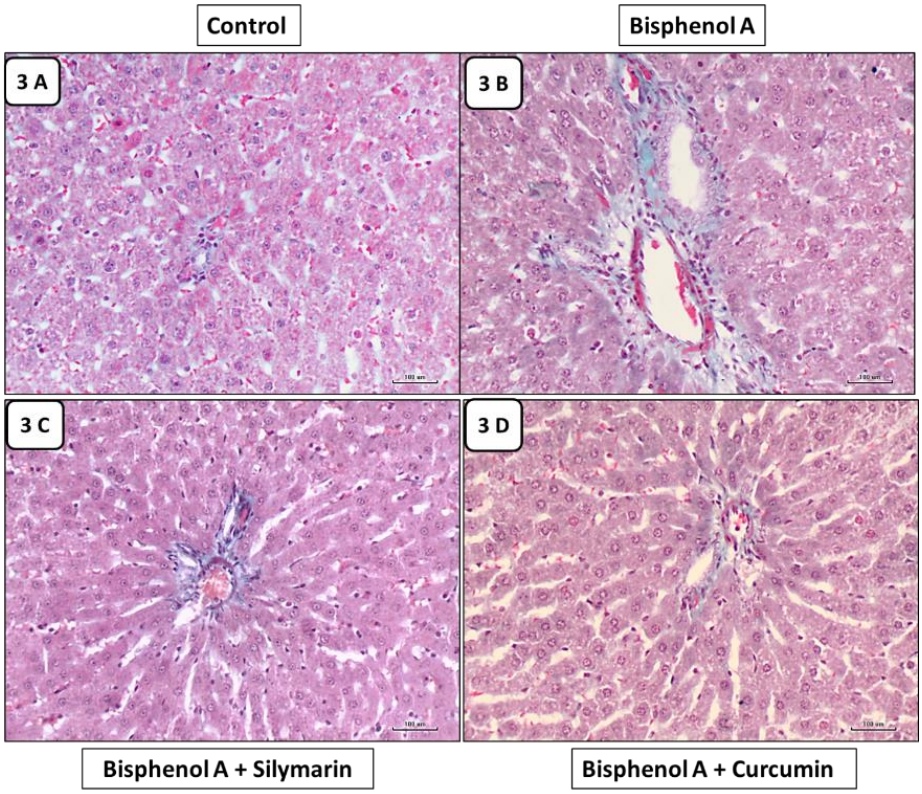

Figure [3]: Photomicrographs of M. Trichrome stained liver sections for the caspase-3 [A] control group showing weakest deposition of collagen fibers while the highest expression of collagen fibers in Bisphenol A group [B]; weak deposition of collagen fibers in treated groups with Bisphenol A + Silymarin/Curcumin group [C, D]. A: Control group; B: Bisphenol A group; C: Bisphenol A + Silymarin group; and D: Bisphenol A + Curcumin group; [M. Trichrome stain. X400] Scale bars, 100 µm.

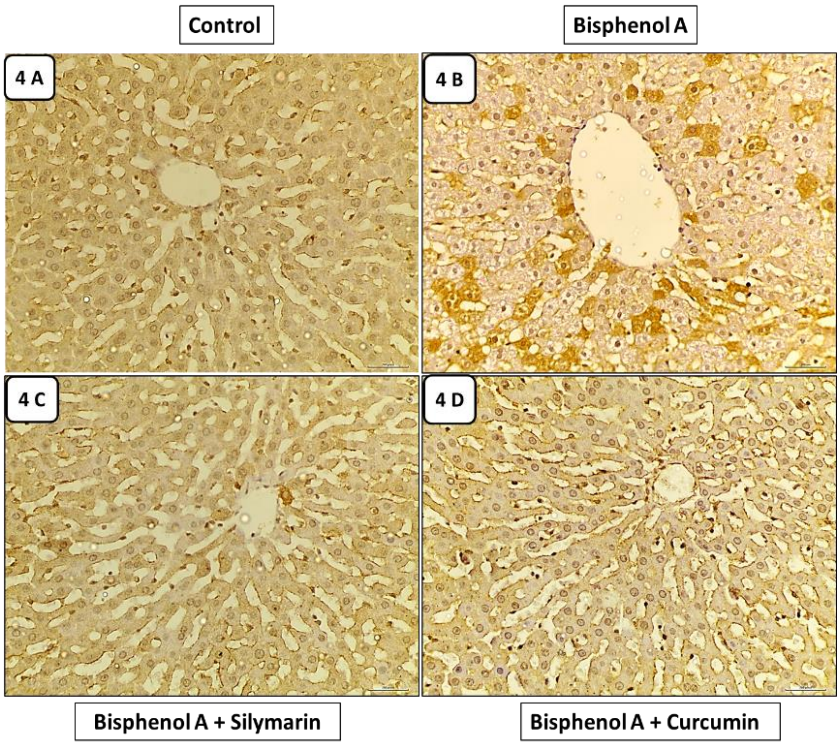

Figure [4]: Photomicrographs of Immunostained liver sections for the caspase-3 [A] control group showing weakest expression of caspase-3. highest expression of caspase-3 in Bisphenol A group [B]; weak expression of caspase-3 in treated groups with Bisphenol A + Silymarin/Curcumin group [C, D]. A: Control group; B: Bisphenol A group; C: Bisphenol A + Silymarin group; and D: Bisphenol A + Curcumin group. [Caspase 3 immune stain. X400] Scale bars, 200 pixels

DISCUSSION

Bisphenol A is a commonest environmental pollutant. It is commonly used in different industries [e.g., epoxy resins, food containers, and many plastic products]. This led to high BPA concentrations in several body fluids [e.g., blood, amniotic fluid, and breast milk]. In addition, it is deposited in different organs [10]. Bisphenol-A is usually metabolized by the liver. This exposes the liver to the toxic actions of BPA through induction of oxidative stress [11,12]. Preventions of such damage is crucial to keep the health of liver. The current experiment aimed to assess the preventive or ameliorative effects of silymarin or curcumin on the hepatotoxicity induced by BPA in albino rats. Results revealed that, bisphenol A toxicity was associated with a significant increase of liver enzymes than the control group. Previous research has reported elevated liver enzymes on exposure to BPA, which reflected a damage of liver tissues [13]. The cellular damage of the liver is associated with a reduction of the permeability of cell membranes. Thus, increasing the serum levels of transaminases. The high levels of ALP may be due to cholestasis and indicating hepatocellular damage [14].

In the current work, the cellular hepatic damage suggested by increased liver enzymes on exposure to BPA was confirmed by the microscopic examination of hepatic sections. It was reflected as hepatocyte destruction with marked vacuolated cytoplasm, deeply stained shrunken nuclei and dilated congested blood sinusoids with abundant Kupffer cells. The portal area had a marked cellular infiltration, congested bile duct and hepatic arteriole. This was in line with a previous study reported that BPA-induced hepatotoxicity and cardiotoxicity in rats [15]. Nakagawa and Tayama [16] also reported hepatocyte cytotoxicity, cell damage and lysis in BPA-exposed rats.

In the present study, the liver fibrosis was assessed by Masson trichrome stain for detection of collagen deposition in hepatocytes. The oral administration of BPA was associated with hepatic fibrosis in the form of increased collagen deposition in the liver tissue. These results come in accordance with Elswefy et al. [17], who reported liver fibrosis in BPA-treated rats. They also reported that BPA exerted this harmful action through increased production of the proinflammatory cytokine [IL-1b] and reduction of the hepatocyte antioxidants [GSH, CAT] and hepatocyte fibrotic markers.

In the current work, the associated inflammation in the liver exposed to BPA was detected by assessment of the inflammatory markers [TNF-α, IL-6, IL-1β, and IL-8]. These substances were significantly increased. A recent study reported that BPA exposure was associated with significantly increased levels of NF-κB, TNF-α, IL-6, IL-1β, and COX-2 [10]. Those pro-inflammatory cytokines are indicators of acute inflammatory response, liver fibrosis and other ROS-connected disorders [18].

In this study, caspase-3 was used to assess the liver apoptosis. Results revealed that, oral BPA administration stimulated an increase in caspase-3 immunoreactivity. A previous animal study examined the oral exposure of rats to BPA showed a significant increase in the caspase-3 levels [17]. The mechanisms of BPA-induced apoptosis

may be explained by mitochondrial actions. These actions play a chief role in induction of apoptosis through liberating intermembrane space proteins, like cyto-chrome-c, a principal mediator of apoptosis by the cytoplasmic activation of caspases [19].

Oxidative stress had a significant role in apoptosis. Consistent with this assumption, BPA was associated with a significant increase of oxidative stress and stimulate hepatocyte cellular apoptosis. This was confirmed in the current work by a notable decrease in the activity of antioxidant enzymes [e.g, CAT, SOD, and GPX] and remarkable increase in MDA and H_2O_2 levels. This was in agreement with the results of recent researches which reported that BPA exposure decrease the activation of antioxidant enzymes [10, 20]. These antioxidants offer a cellular defense action against ROS-induced oxidative stress damage [21]. Also, the harmful effects of BPA might be related to increased production of reactive intermediate substances during BPA metabolism [13]. Moreover, several researches have reported that the exposure to BPA induces free radicals as [MDA and H_2O_2], which usually leads to disruption of antioxidant enzymes [CAT, SOD, and GPX] defense mechanism [2, 11].

Those antioxidant markers have a main role in the cellular defense mechanism against oxidative stress produced by ROS. This could be explained by the following: CAT catalyzes the hydrogen peroxide into oxygen and water. Thus, defends hepatocytes against oxidative injury of hydroxyl radicals [22]; SOD plays a protective role against damage of free radicals and eradicates them by decreasing their toxicity [23]; GPX is a selenoenzyme that contribute in minimizing levels of H_2O_2 and fatty acid hydroperoxides. Thus, protecting the mammalian cells against oxidative stress as well as other peroxides [24]. Lastly, MDA is an end product of polyunsaturated fatty acids peroxidation in the cellular membrane. The MDA high level is a chief indicator of lipid peroxidation. However, the level of MDA indirectly reveals the degree of cellular destruction and tissue damage [25]. Results of the current work confirmed by previous study indicating that, curcumin and silymarin are natural products, with high levels of antioxidants, and used to protect against different environmental toxins-induced hepatocellular damage due to increased ROS [26].

The concomitant use of silymarin or curcumin with BPA revealed a potential hepatocyte protective effect. This was evident by a significant reduction of liver enzyme levels. The protective actions of curcumin and silymarin could be linked to preservation of cell membrane integrity due to antioxidant activity. The biochemical results confirmed by histopathology. These results are in accordance with recent studies showed a significant ameliorative effect of curcumin on BPA-induced hepatotoxic effects [25,27].

The current study results showed potential preservation of normal hepatic architecture with the concomitant use of curcumin or silymarin with BPA. This was ascribed to antioxidant effects of both substances. This was in agreements with Uzunhisarcikli and Aslanturk [25], and Zaulet et al. [28]. In addition, the current work revealed that curcumin and silymarin has anti-inflammatory effects through decreased production of inflammatory cytokines. These results coincide with the previous studies showed hepatoprotective effects of curcumin and silymarin through anti-inflammatory, antioxidant and antimetabolite actions [29,30]. Curcumin strongly obstructs the production of ROS through prevention of hydroxyl radical and superoxide anion formation [31].

In the current research, the anti-apoptotic activity of curcumin and silymarin was confirmed quantitatively by the expression of caspase-3. BPA exposure was associated with significant production, while curcumin and silymarin concomitant administration significantly alleviates the BPA-induced apoptosis. However, curcumin has a more anti-apoptotic effect than silymarin. These results are in line with a previous studies revealed a strong anti-apoptotic effect of curcumin by reducing the immune-expression of caspase-3 [8, 32].

Conclusion: BPA causes hepatotoxic effects through disturbance of the redox system and increased ROS production leading to a condition of oxidative stress. Oral administration of curcumin or silymarin ameliorates the harmful effects of BPA by anti-inflammatory, anti-apoptotic and antioxidant effects.

Financial and Conflict of interest disclosure:

None

REFERENCES

1. Lin N, Ma D, Liu Z, Wang X, Ma L. Migration of bisphenol A and its related compounds in canned seafood and dietary exposure estimation. Food Quality and Safety 2022; xxx-xxx [Article in Press]. doi: 10.1093/fqsafe/fyac006

2. Wang J, Zhu H, Zhang C, Wang H, Yang Z. Protective effects of baicalein against cadmium-induced oxidative stress in rat testes. Pak Vet J 2019; 39[2], 216–220. doi: 10.29261/pakvetj/2019.025.

3. Fenichel P, Chevalier N, Brucker-Davis F. Bisphenol A: an endocrine and metabolic disruptor. Ann Endocrinol [Paris]. 2013 Jul;74[3]:211-20. doi: 10.1016/j.ando.2013.04.002.

4. Rochester JR. Bisphenol A and human health: a review of the literature. Reprod Toxicol. 2013 Dec; 42:132-55. doi: 10.1016/j.reprotox.2013.08.008.

5. Wang Y, Du X, Wang D, Wang J, Du J. Effects of Bisphenol A exposure during Pregnancy and lactation on Hippo-campal Function in Newborn Rats. Int J Med Sci. 2020 Jul 6;17[12]:1751-1762. doi: 10.7150/ijms.47300.

6. Mahdavinia M, Khorsandi L, Alboghobeish S, Samimi A, Dehghani MA, Zeidooni L. Liver histopathological alteration and dysfunction after bisphenol-A in male rats and protective effects of naringin. Avicenna J Phytomed. 2021;11[4]:394-406. doi: 10.22038/AJP.2021.17649.

7. Fadishei M, Ghasemzadeh Rahbardar M, Imenshahidi M, Mohajeri A, Razavi BM, Hosseinzadeh H. Effects of Nigella sativa oil and thymoquinone against bisphenol A-

induced metabolic disorder in rats. Phytother Res. 2021 Apr;35[4]:2005-2024. doi: 10.1002/ptr.6944.

8. Ahmad MM, Rezk NA, Fawzy A, Sabry M. Protective effects of curcumin and silymarin against paracetamol induced hepatotoxicity in adult male albino rats. Gene. 2019 Sep 5; 712:143966. doi: 10.1016/j.gene.2019.143966.

9. Hüttl M, Markova I, Miklankova D, Zapletalova I, Poruba M, Racova Z, Vecera R, Malinska H. The Beneficial Additive Effect of Silymarin in Metformin Therapy of Liver Steatosis in a Pre-Diabetic Model. Pharmaceutics. 2021;14[1]:45. doi: 10.3390/pharmaceutics14010045.

10. Ijaz MU, Shahab MS, Samad A, Ashraf A, Al-Ghanim K, Mruthinti SS, Mahboob S. Tangeretin ameliorates bisphenol induced hepatocyte injury by inhibiting inflammation and oxidative stress. Saudi J Biol Sci. 2021; xx: xx. doi: 10.1016/J.SJBS. 2021.11.007.

11. Kim JH, Lee MR, Hong YC. Modification of the association of bisphenol A with abnormal liver function by polymorphisms of oxidative stress-related genes. Environ Res. 2016;147: 324-30. doi: 10.1016/j.envres.2016. 02.026.

12. Thoene M, Rytel L, Dzika E, Włodarczyk A, Kruminis-Kaszkiel E, Konrad P, Wojtkiewicz J. Bisphenol A Causes Liver Damage and Selectively Alters the Neurochemical Coding of Intrahepatic Parasympathetic Nerves in Juvenile Porcine Models under Physiological Conditions. Int J Mol Sci. 2017;18[12]:2726. doi: 10.3390/ijms 18122726.

13. Vagvala SH, O'Connor SD. Imaging of abnormal liver function tests. Clin Liver Dis [Hoboken]. 2018 Jun 5;11[5]:128-134. doi: 10.1002/cld.704.

14. Wang X, Gao M, Wang Z, Cui W, Zhang J, Zhang W, Xia Y, Wei B, Tang Y, Xu X. Hepatoprotective effects of oridonin against bisphenol A induced liver injury in rats via inhibiting the activity of xanthione oxidase. Sci Total Environ. 2021 May 20; 770:145301. doi: 10.1016/ j. scitotenv.2021.145301.

15. Eweda SM, Newairy ASA, Abdou HM, Gaber AS. Bisphenol A-induced oxidative damage in the hepatic and cardiac tissues of rats: The modulatory role of sesame lignans. Exp Ther Med. 2020 Jan;19[1]:33-44. doi: 10.3892/etm.2019.8193.

16. Nakagawa Y, Tayama S. Metabolism and cytotoxicity of bisphenol A and other bisphenols in isolated rat hepatocytes. Arch Toxicol. 2000 Apr;74[2]:99-105. doi: 10.1007/ s002040050659.

17. Elswefy SE, Abdallah FR, Atteia HH, Wahba AS, Hasan RA. Inflammation, oxidative stress and apoptosis cascade implications in bisphenol A-induced liver fibrosis in male rats. Int J Exp Pathol. 2016 Oct;97[5]:369-379. doi: 10.1111/iep.12207.

18. Kandemir FM, Yildirim S, Kucukler S, Caglayan C, Mahamadu A, Dortbudak MB. Therapeutic efficacy of zingerone against vancomycin-induced oxidative stress, inflammation, apoptosis and aquaporin 1 permeability in rat kidney. Biomed Pharmacother. 2018 Sep; 105:981-991. doi: 10.1016/j.biopha.2018.06.048.

19. Vaux DL. Apoptogenic factors released from mitochondria. Biochim Biophys Acta. 2011 Apr;1813[4]:546-50. doi: 10.1016/j.bbamcr.2010.08.002.

20. Meli R, Monnolo A, Annunziata C, Pirozzi C, Ferrante MC. Oxidative stress and BPA toxicity: An antioxidant approach for male and female reproductive dysfunction. Antioxidants [Basel]. 2020;9[5]: 405. doi: 10.3390/antiox 9050405.

21. Latif M, Faheem M. Study of Oxidative Stress and Histo-Biochemical Biomarkers of Diethyl Phthalate Induced Toxicity in a Cultureable Fish, Labeo rohita. Pak Vet J. 2020; 40[2]: 202-208. doi:10.29261/pakvetj/2019.108

22. Ansari MA, Raish M, Ahmad A, Alkharfy KM, Ahmad SF, Attia SM, Alsaad AM. Sinapic acid ameliorate cadmium-induced nephrotoxicity: In vivo possible involvement of oxidative stress, apoptosis, and inflammation via NF-κB downregulation. Environ Toxicol Pharmacol. 2017; 51: 100-107. doi: 10.1016/j.etap.2017.02.014.

23. Stinghen AE, Chillon JM, Massy ZA, Boullier A. Differential effects of indoxyl sulfate and inorganic phosphate in a murine cerebral endothelial cell line [bEnd.3]. Toxins [Basel]. 2014 Jun 4;6[6]:1742-60. doi: 10.3390/toxins6061742.

24. Jurjus AR, Khoury NN, Reimund JM. Animal models of inflammatory bowel disease. J Pharmacol Toxicol Methods. 2004;50[2]:81-92. doi: 10.1016/j.vascn.2003. 12.002.

25. Uzunhisarcikli M, Aslanturk A. Hepatoprotective effects of curcumin and taurine against bisphenol A-induced liver injury in rats. Environ Sci Pollut Res Int. 2019 Dec; 26[36]:37242-37253. doi: 10.1007/s11356-019-06615-8.

26. Nagai K, Fukuno S, Oda A, Konishi H. Protective effects of taurine on doxorubicin-induced acute hepatotoxicity through suppression of oxidative stress and apoptotic responses. Anticancer Drugs. 2016 Jan;27[1]:17-23. doi: 10.1097/CAD.0000000000000299.

27. Elghannam AA, Bahr HI, Abou El Ftouh AA. Synergistic Hepatoameliorative Potential of Silymarin and Ethanolic Extract of Jasonia Montana Versus Bisphenol. Indian J Applied Res. 2017; 7[8]: 211–217. DOI: 10.36106/ijar

28. Zaulet M, Kevorkian SEM, Dinescu S, Cotoraci C, Suciu M, Herman H, Buburuzan L, Badulescu L, Ardelean A, Hermenean A. Protective effects of silymarin against bisphenol A-induced hepatotoxicity in mouse liver. Exp Ther Med. 2017 Mar;13[3]:821-828. doi: 10.3892/ etm.2017.4066.

29. Jang H-Y, Kong H-S, Choi B-Y, Shin J-S, Cheong H-T, Kim J-T, Park I-C, Park C-K, Yang B-K. Protective Effects of Silymarin against the Toxicity of Bisphenol A [BPA] on Boar Sperm Quality. J Embryo Transfer 2011; 26[4]: 257–263.

30. Yu C, Mei XT, Zheng YP, Xu DH. Zn[II]-curcumin protects against hemorheological alterations, oxidative stress and liver injury in a rat model of acute alcoholism. Environ Toxicol Pharmacol. 2014 Mar;37[2]:729-37. doi: 10.1016/ j. etap.2014.02.011.

31. Messarah M, Amamra W, Boumendjel A, Barkat L, Bouasla I, Abdennour C, Feki AE. Ameliorating effects of curcumin and vitamin E on diazinon-induced oxidative damage in rat liver and erythrocytes. Toxicol Ind Health. 2013;29[1]:77-88. doi: 10.1177/ 0748233712446726.

32. Hu B, Colletti LM. CXC receptor-2 knockout genotype increases X-linked inhibitor of apoptosis protein and protects mice from acetaminophen hepatotoxicity. Hepatology. 2010 Aug;52[2]: 691-702. doi: 10.1002/ hep.23715.

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