Review Article

Adverse Effects of Bisphenol A on the Liver and Its Underlying Mechanisms: Evidence from In Vivo and In Vitro Studies

Al-Salihi Ahmed Rashid Abdulhameed,1 Vuanghao Lim2, Hasnah Bahari1, Boon Yin Khoo3, Muhammad Nazrul Hakim Abdullah4, Jun Jie Tan2, and Yoke Keong Yong1

1Department of Human Anatomy, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia
2Advanced Medical and Dental Institute, Universiti Sains Malaysia, Bertam, 13200 Kepala Batas, Penang, Malaysia
3Institute for Research in Molecular Medicine, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia
4Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia

Correspondence should be addressed to Jun Jie Tan; jjtan@usm.my and Yoke Keong Yong; yoke_keong@upm.edu.my

Received 23 March 2022; Revised 6 July 2022; Accepted 28 July 2022; Published 16 August 2022

Academic Editor: Aleksandra Buha

Copyright © 2022 Al-Salihi Ahmed Rashid Abdulhameed et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Bisphenol A (BPA), also known as 2,2-bis(four-hydroxyphenyl)propane, is a popular artificial organic molecule that is utilised in polycarbonate plastics and epoxy resins as an intermediate sort of combination product [1]. BPA is also known as an endocrine disruptor for its ability to mimic the repercussions of endogenous hormones [2]. It represented a global market share of 15 billion pounds in 2013, and it is one of the largest manufacturing chemicals within the global synthetics industry in volume [3]. BPA is used for manufacturing epoxy resins, which are found in plastic food containers, piping, wire insulations, and healthcare consumables. Due to the increased popularity of the production and usage of this product, BPA has been infiltrated and released into our ecosystem and food chain. Therefore, organisms, including humans, are constantly exposed to BPA. A plethora of recent research has shown that a significant population has measurable amounts of BPA in either urine or serum samples, but the importance of existing levels of sensitivity to the toxicological consequences of BPA remains fiercely contested [4–11].

The prime cause of BPA contamination is from the leaching out of plastic products. The sources of BPA ingestion may vary according to environmental, social, and age factors.
including baby and beverage bottles, as well as the repeated use of containers, food cans, and even medical equipment such as polycarbonate hemodialysis equipment [12, 13]. Ingestion of these contaminated foods and liquids may bring harm to human health, especially the liver. The liver is critical in the control of several physiological processes of the body, and it is the primary organ engaged in the detoxification of a variety of medications and xenobiotics. Due to that, it plays an important role in the elimination of ingested BPA. It was believed that when unconjugated BPA (the active form of BPA) is taken orally, it is promptly conjugated in the liver and subsequently eliminated via bile or urine [14]. However, the β-glucuronidase enzyme, which is present within many tissues, is able to deconjugate BPA [14], and this might result in the bioaccumulation of BPA in the body. In fact, a recent study reported that most plasma BPA is bound to serum protein and the accumulation of BPA was about three times higher in fat compared to other tissues [15]. Numerous evidences from preclinical studies have also proven that the administration of BPA in animals was correlated with the alteration of blood lipid profile and interfered with the oxidant/antioxidant mechanism in the liver [16, 17], which may eventually lead to liver damage.

Since BPA might influence several biological processes associated with liver function, which may lead to liver damage, this review is aimed at providing a concise summary of the data regarding the detrimental effects of BPA exposure on the liver. The analysis of numerous references was considered, many of which included cellular and animal experiments and offered a detailed summary on the topic at hand.

2. Methodology for Data Collection

In online research databases like PubMed, Web of Science, MEDLINE, Google Scholar, and Science Direct, articles on the effect of BPA on kidney were searched for using specific keywords such as “bisphenol a,” “BPA,” “kidney,” “in vitro,” “in vivo,” and “animal model.” These articles were then downloaded.

3. Experimental Evidence of BPA Damage to the Liver, In Vivo Model

3.1. BPA Changed the Level of Liver Enzyme. The liver is the largest internal organ, and it performs many functions, including metabolizing and detoxifying waste products, synthesizing proteins, and maintaining a stable blood glucose level. In order to carry out the abovementioned activities, liver enzymes play the most important role here to speed up these chemical reactions. However, changes in the level of liver enzymes can suggest liver injury or the alteration of bile supply [18]. For instance, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are the most sensitive indicators of hepatocyte injury [19]. These enzymes will leak into the bloodstream when the hepatocytes are injured or when changes occur in the cell membrane permeability [19]. BPA is known as an endocrine-disrupting agent, and it is also often considered toxic to the body, inducing oxidative stress by impacting vital organs. On top of that, some studies have shown that increased reactive oxygen species (ROS) levels contribute to the oxidation of unsaturated fatty acid cellular constituents and otherwise cause cell apoptosis and degeneration [20].

Some studies investigated the effect of BPA on the liver enzyme in vivo (Table 1). The range of dosages and the duration of exposure time used in the studies vary, from the lowest of 1.0 μg/kg, up to the highest of 120 mg/kg, and the shortest of 1 hour, to the longest of 140 days, respectively. The mode of administration of BPA is mainly via oral but could also be based on intraperitoneal and intravenous injections. Based on the data obtained, BPA significantly affects liver enzyme activity, where it might be able to prime the liver damage. According to Moon and his team [21], a single injection of 1.2 mg/kg b.w./day of BPA significantly elevated AST and ALT levels within 24 hr compared to control in specific pathogen-free C57BL/6 male mice. Hassan et al. reported that 10 and 50 mg/kg of BPA significantly increased serum ALT, ALP, and bilirubin compared to control when albino rats received BPA once daily for up to 4 weeks [22]. On top of that, another two studies also documented that AST and ALT levels significantly increased in BPA-treated rats which received a daily dose of 10 and 50 mg/kg for a duration of 8 weeks compared to control [23, 24]. Moreover, rats treated with 10 mg/kg of BPA for a duration of 60 days also showed significantly increased AST, ALT, and PAL levels when compared to the control group [25]. Interestingly, some studies reported that BPA does not significantly affect liver enzyme activities. For instance, rats treated with 50 and 500 μg/kg/day of BPA for 20 weeks did not induce alteration of AST and ALT levels compared to control [26]. Furthermore, Mourad and Khadayw [27] also proved that 10 mg/kg/day of BPA showed no significant difference compared to control in AST and ALT activities in 6- or 10-week duration of treatment. However, 25 mg/kg/day (6 weeks of treatment) of BPA showed a significant elevation of AST and ALT activities compared to control. BPA at 4 mg/kg did not show any effect in rat models of hepatic I/R injury after 24 hours postreperfusion [28]. The differences in the results obtained by different researchers could be due to differences in terms of animal strains/species, gender of the animal, dosage, and treatment duration, as well as environmental factors.

3.2. Consumption of BPA Altered the Histomorphology of Liver Cells. The harmful effects of BPA on the liver have all been well documented. Studies on several animal models have clearly shown that exposure to BPA, whether short- or long-term, can cause direct hepatotoxicity in the aspect of histomorphology (Table 2). According to Zaulet and his team [34], CD-1 mice treated with 200 mg/kg b.w. daily of BPA orally for only 10 days significantly induced necrotic changes in hepatocytes. The changes were particularly pronounced in the centrilobular area. Inflammatory cell infiltration and vascular congestion were observed in the BPA-treated group compared to the control. Similar results were observed in another study. However, the concentration of BPA was reduced to 130 mg/kg b.w./day for four weeks [35]. On the other hand, studies from the Peerapanyasut Laboratory using 5 and 50 mg/kg b.w./day of BPA in rats for five weeks provided some evidence for a causative role for BPA in liver toxicity, particularly in rats receiving BPA 50 mg/kg b.w./day [29]. Furthermore, Peerapanyasut and his team [31] further investigated the harmful effects of
| No. | Type of animal | Dose/ concentration | Vehicles | Mode of administration | Duration of treatment | Mode of administration | Liver function test results |
|-----|----------------|---------------------|----------|------------------------|----------------------|------------------------|-----------------------------|
| 1   | Swiss rats     | 10 mg/kg b.w./day   | Water    | Oral                   | 60 days/daily/once   | Increase in AST, ALT, PAL, LDH, and TNF-alpha [25] |
| 2   | Male Wistar rats | 5 and 50 mg/kg b.w./day | Corn oil | Oral                   | 5 weeks/daily/once   | 5 mg/kg b.w.-day—not significant compared to control in both AST and ALT; significant compared to control in both AST and ALT at concentration of 25 mg/kg b.w./day; 24 hr pretreatment in rat model of hepatic I/R injury [28] |
| 3   | Male Sprague-Dawley rats | 4 mg/kg b.w./day DMSO, diluted with saline | IV       | Oral                   | 24 hours/once        | No significant difference in BPA group compared to control after 24 hr postreperfusion in rat model of hepatic I/R injury [28] |
| 4   | Male C57BL/6 mice | 1.0, 10, 50, and 250 μg/kg b.w./day | PEG      | Oral                   | 35 days/daily/once   | No significant difference compared to control at all concentration for P4H, IL-1beta, PLA 2, AST, ALT. However, there was significant elevation of ALT at 50 μg/kg b.w./day [29] |
| 5   | Male Wistar rats | 5 and 50 mg/kg b.w./day | Corn oil | Oral                   | 5 weeks/daily/once   | Significant elevation of AST and ALT in the renal ischemia and reperfusion animals when exposed to BPA at concentration of 5 and 50 mg/kg b.w./day [31] |
| 6   | Male Wistar rats | 50 and 500 μg/kg b.w./day | Water    | Oral                   | 20 weeks             | No significant difference compared to control at all concentration for AST and ALT [32] |
| 7   | Male Wistar rats | 25 and 50 mg/kg b.w./day | Normal saline | IP         | 25 mg/kg b.w./day (6 weeks); 10 mg/kg b.w./day (6 weeks and 10 weeks); 5 days a week | Significant elevation of AST and ALT [32] |
| 8   | Male Wistar rats | 0.1, 1, 10, and 50 mg/kg b.w./day | Ethanol in water | Oral | 10 mg/kg b.w./day (6 weeks); 5 mg/kg b.w./day (6 weeks and 10 weeks); 5 days a week | Significant elevation of AST and ALT [32] |
| 9   | Male Wistar rats | 25 and 125 mg/kg b.w./day | Olive oil | Oral                   | 8 weeks/daily/once   | No significant difference compared to control at all concentration for AST and ALT [32] |
| 10  | Male Wistar rats | 10 mg BPA/kg b.w./day | Corn oil | Oral                   | 8 weeks/daily/once   | All BPA dosages reduced ALP and AST serum levels except ALT [24] |
| 11  | Specific pathogen-free C57BL/6 male mice | 1.2 mg/kg b.w./day | Normal saline | IP         | 1, 6, and 24 hr | No difference after 5 days of treatment (ALT, AST, 60 ± 14 U/L vs. 57 ± 10 U/L, P > 0.05), although serum AST levels showed an increasing tendency in BPA-treated mice (30 ± 4 U/L vs. 48 ± 20 U/L, P < 0.05) [21] |
| No. | Type of animal | Dose/concentration | Vehicles | Mode of administration | Duration of treatment | Liver function test results | Reference |
|-----|----------------|--------------------|----------|------------------------|----------------------|-----------------------------|------------|
| 13  | Specific pathogen-free C57BL/6 male mice | 1.2 mg/kg b.w./day | Normal saline | IP | 1, 6, and 24 hr | Within 24 hr of a single injection of 1.2 mg/kg b.w./day of BPA, both AST and ALT levels significantly increased ($P = 0.03$ and $0.01$, respectively) | [21] |
| 14  | Virgin female (270–300 g) and male (350–400 g) genitor Wistar rats were | 50 μg/kg b.w./day | Corn oil | Oral | GD 0 to the end of lactation at postnatal day 21 | Perinatal exposure to BPA only resulted in a minor increase in serum ALT levels at 3 and 15 weeks but a significant increase at 21 weeks compared to the control in offspring | [33] |
Table 2: Summary of selected studies on the effect of BPA-induced liver histomorphological changes. Abbreviation: b.w.: body weight; PEG: polyethylene glycol; IV: intravenous.

| No. | Type of animal    | Dose/concentration | Vehicles      | Mode of administration | Duration of treatment | Histology result                                                                                                                                                                                                                                                                                                                                 |
|-----|-------------------|--------------------|---------------|------------------------|----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1   | Swiss rats        | 10 mg/kg b.w./day  | Water         | Oral                   | 60 days/daily/once   | BPA group showed steatosis and inflammation. H&E, and oil red O-stained sections showed early indications of hepatic inflammation with Kupffer cell infiltration and steatosis (lipid droplet buildup in hepatocyte cytoplasm). Sinusoidal spaces grew larger, cells lost their typical polygonal form, acidophilus reduced, and hepatocyte cord structure deteriorated. The hepatocyte cytoplasm had a significant number of foamy-like vacuolar degeneration and a big number of apoptotic cells. Oil droplets produced in hepatocytes and the perisinusoidal region were concentrated. The centralis and portal area fibre density and sinusoidal space dilatations were enhanced. The reticular fibre distribution indicated liver fibrosis. |
| 2   | Sprague-Dawley    | 25 mg/kg b.w./day  | Sesame oil    | Oral                   | 60 days/daily/once   | Sinusoidal spaces grew larger, cells lost their typical polygonal form, acidophilus reduced, and hepatocyte cord structure deteriorated. The hepatocyte cytoplasm had a significant number of foamy-like vacuolar degeneration and a big number of apoptotic cells. Oil droplets produced in hepatocytes and the perisinusoidal region were concentrated. The centralis and portal area fibre density and sinusoidal space dilatations were enhanced. The reticular fibre distribution indicated liver fibrosis. |
| 3   | Male Wistar rats  | 5 and 50 mg/kg b.w./day | Corn oil    | Oral                   | 5 weeks/daily/once   | BPA 50 mg/kg showed a decrease in mitochondrial number with asymmetric mitochondrial swelling. LD BPA group revealed abnormally enlarged sinusoidal cavity, KC, necrotic hepatocytes, granularly degraded hepatocytes, and dilated sinusoids. Massive hepatocytes with cytoplasmic vacuolation or granulation and prominent Kupffer cells were seen in the BPA 100 mg/kg group. |
| 4   | Prepubertal female | 10 and 100 mg/kg b.w./day | Palm oil    | Oral                   | 6 weeks/daily/once   | Necrotic hepatocytes in the centrilobular region. Moreover, evident was inflammation and vascular congestion. BPA exposure during pregnancy influenced hepatic fat buildup in adult male offspring. Male offspring treated with BPA gained weight and had higher hepatic TG levels when subjected to HFD. BPA enhanced the amount of HFD-induced hepatic lipid droplets. In BPA-exposed liver tissue, electron imaging indicated an increase in intracellular lipid corpuscles. |
| 5   | Male CD-1 mice    | 200 mg/kg b.w./day | Corn oil      | Oral                   | 10 days/daily/once   | BPA administration was initiated at E7.5, before the development of the embryonic liver and resumed up until E16.5. |
| 6   | Adult C57BL/6j mice | 1, 10, 100, and 1000 μg/kg b.w./day | Corn oil    | Oral                   | 35 days/daily/once   | Liver appeared slight edema in the BPA group, but no other significant pathological changes. |
| 7   | Male Sprague-Dawley rats | 4 mg/kg b.w./day | Dissolve in DMSO, diluted with saline | IV                    | 24 hr/once           | I/R and I/R+BPA groups had significant necrosis, nuclear pyknosis, and intercellular border loss. |
| 8   | Male Wistar rats  | 130 mg/kg b.w./day | Olive oil     | Oral                   | 4 weeks (28 days)    | BPA-exposed rats exhibited dilated sinusoids, inflammatory cell infiltration, congestion, and necrosis. |
| 9   | Male C57BL/6 mice | 1.0, 10, 50, and 250 μg/kg b.w./day | PEG         | Oral                   | 35 days/daily/once   | Liver appeared slight edema in the BPA group, but no other significant pathological changes. |
| 10  | Male Wistar rats  | 5 and 50 mg/kg b.w./day | Corn oil    | Oral                   | 5 weeks/daily/once   | BPA-treated RIR group (BIR) showed dilated sinusoids, centrilobular congestion, and lymphocyte infiltration in the portal tract. |
BPA on acute kidney injury-induced remote organ injury in the liver. Based on the data obtained, BPA significantly altered the liver cell structure where dilated sinusoids, centrilobular congestion, leukocyte infiltration in portal tracts, and focal hepatocellular necrosis were observed [31]. Additionally, significant pathological changes in liver cells were also reported in several other studies [25, 30, 36, 37]. More recently, Long and his team [38] documented that gestational exposure to BPA leads to a sex-dependent effect on hepatic lipid accumulation in adult male offspring, and the formation of intracellular lipid corpuscles in the BPA-exposed liver tissue, as revealed by electron microscopy. This evidence suggests deleterious effects on liver function after long-term BPA consumption.

### 4. Mechanism Study of BPA on Liver

Previous studies have unravelled the possible mechanisms underlying the detrimental effects of BPA, particularly on the liver, including evidence derived from in vivo and in vitro experiments, among which are further elaborated hereafter.

#### 4.1. Injury from Oxidative Stress

Reactive oxygen species (ROS) are known to have an important role in the physiological functions of the human body. It serves as a second messenger in various cell signalling pathways that control the homeostasis of normal cellular functions [39] and also acts as a promoter of natural defences by killing bacteria [40]. However, when the production of ROS exceeds the capacity of antioxidant defences, oxidative stress is inflicted and can negatively affect the biological tissue function and structural integrity. These events will eventually result in defects and diseases. There are several ways how ROS causes cellular damage, such as damaging DNA through strand breaks and base oxidation, which leads to cell death. The oxidation of proteins results in their inactivation, which eventually resulted in cell injury or death. Moreover, ROS that was produced causes oxidative damage to DNA, which can be observed through the TUNNEL assay [42].

#### Table 3: Summary of selected studies on the mechanism of BPA-induced liver damage. Abbreviations: b.w.: body weight; GD: gestation day; IP: intraperitoneal; NA: not applicable.

| No. | Type of animal/cells | Dose/concentration | Mode of administration | Duration of treatment | Study type | Mechanisms | Reference |
|-----|----------------------|--------------------|------------------------|----------------------|------------|------------|-----------|
| 1   | Specific pathogen-free C57BL/6 male mice | 1.2 mg/kg b.w./day | IP | 1, 6, and 24 hr | In vivo | Mitochondria dysfunction, increased inflammatory mediator production | [21] |
| 2   | Male Wistar albino rats | 0.1, 1, 10, and 50 mg/kg b.w./day | Oral | 4 weeks/daily/once | In vivo | Increased oxidative stress | [22] |
| 3   | Male Wistar albino rats | 50 mg/kg b.w./day | Oral | 8 weeks/daily/once | In vivo | Increased inflammatory mediator production | [23] |
| 4   | Virgin female (270–300 g) and male (350–400 g) genitor Wistar rats were | 50 μg/kg b.w./day | GD 0 to the end of lactation at postnatal day 21 | In vivo | Mitochondria dysfunction | [33] |
| 5   | Male Sprague-Dawley rats | 2, 10, and 50 mg/kg b.w./day | IP | 30 days; administered every 48 hr | In vivo | Increased oxidative stress | [42] |
| 6   | Male albino rats (Wistar strain) | 150, 250, and 500 mg/kg b.w./day | Oral | 14 days/daily/once | In vivo | Mitochondria dysfunction | [47] |
| 7   | Male CD-1 mice | 50 μg/kg b.w./day | Oral | 10 weeks/daily/once | In vivo | Mitochondria dysfunction, increased oxidative stress, increased mitochondrial mediator production | [48] |
| 8   | NCTC Clone 1469 | 100 μM | NA | 48 hr | In vitro | Endoplasmic reticulum stress, increased oxidative stress | [2] |
| 9   | Female Swiss mice | 70 μg/kg b.w./day | Oral | 3 months/daily | In vivo | Chronic endoplasmic reticulum stress | [56] |
the damaged DNA is not restored successfully and in a timely manner, it could result in teratogenesis, carcinogenesis, mutagenesis, and other irreversible effects [43]. In view of the potential effect of BPA in interfering with redox signalling, an imbalance between oxidants and antioxidants in the liver is inevitable in the presence of BPA.

4.2. Mitochondria Dysfunction. Mitochondria is an essential intracellular organelle that serves as a powerhouse of a cell which generates ATP through oxidative phosphorylation (OXPHOS). It also plays a crucial role in controlling of cell death through the activation of the intracellular signalling cascades or death receptor-mediated pathways [44]. Mitochondria is essential in hepatic metabolism, particularly in maintaining the hepatic energy metabolism, an important hub that serves as a critical site for the production and exchange of metabolic intermediates to maintain well-regulated tissue homeostasis in the human body [44].

Mitochondria is among the important targets of endocrine-disrupting agents, including BPA [33, 45–47]. Previous studies have shown that BPA causes a decrease in ATP synthesis in the mitochondria in insulinoma cells in rats [9]. Khan and his team [47] showed that all concentrations (150, 250, and 500 mg/kg b.w./daily, via oral for 14 days) of BPA affected enzyme activities of hepatocyte mitochondria electron transport chain, by significantly decreasing complexes I, II, II, IV, and V in the electron transport chain reaction [47] (Table 3). Another study also reported that activities of the mitochondria complexes I-IV in the liver of the BPA-treated mice were significantly reduced [48]. Moreover, both mitochondrial respiratory chain complex V production and intercellular ATP content were substantially decreased in the liver tissues following BPA ingestion. Data even showed that BPA enhanced the expression of mitochondrial apoptotic pathway genes, including caspase-3, caspase-8, caspase-9, and caspase-10, as well as the function of caspase enzymes [48]. A similar study by Moon’s laboratory also reported a similar pattern of results [21], albeit the dosages used were much lower than others, which were 0.05 and 1.2 mg/kg b.w/day (below the no observed adverse effect level, NOAEL), administrated intraperitoneally for five days in mice [21]. Both dosages significantly impaired the structure of the hepatic mitochondria, thus leading to hepatic cellular injury, despite the low dosage. Furthermore, 10 or 100 nM of BPA also significantly decreased the oxygen consumption rate, ATP production, and mitochondrial membrane potential in HepG2 cells [21]. Xia et al. also indicated that BPA induced mitochondria-mediated apoptosis in hepatic cells, and BPA acts directly on the mitochondria by altering its ultrastructure, inducing permeability transition and releasing proteins that lead to the activation of apoptosis [33]. Collectively, dietary BPA consumption decreased energy generation in hepatocytes by inhibiting mitochondrial respiratory chain complex function and inducing apoptosis via the mitochondrial pathway.

4.3. Endoplasmic Reticulum Stress. The endoplasmic reticulum functions to synthesize and fold secretory and membrane proteins. It also serves as a special oxidizing compartment that facilitates the folding of membrane and secretory proteins to be transferred to the cell surface, as well as to the lysosomes and Golgi apparatus. These folded secretory and membrane proteins function to regulate body homeostasis, including acting as hormones, enzymes, signalling molecules, calcium ion buffering, and the biosynthesis of phospholipids and cholesterol [49]. Therefore, the effective and efficient functioning of the endoplasmic reticulum is required for most cellular activities and survival. Recent evidence has shown that there is a link between endoplasmic reticulum with apoptosis, which is associated with the accumulation of misfolded or unfolded proteins (endoplasmic reticulum stress) [50–52]. The number of factors that interrupt endoplasmic reticulum function or disturbances in homeostasis processes, which eventually lead to a state in which protein is misfolded, is depletion of endoplasmic reticulum calcium, changes in the redox status, and energy deprivation [53]. Gene defect increased protein traffic through the endoplasmic reticulum environment, and altered posttranslational alteration is all factors that lead to the aggregation of unfolded protein [53]. These events in the endoplasmic reticulum are linked to a variety of pathophysiological disorders, including cell death [54]. Furthermore, an increasing number of endoplasmic reticulum proteins have been shown to affect apoptosis or cell death by interfering with BCL-2 family members or modifying endoplasmic reticulum calcium ion signalling, whereas some endoplasmic reticulum proteins are caspase substrates that may control the apoptosis execution process [55]. Moreover, recent research on the relationship between stress and apoptosis in the endoplasmic reticulum has shown that it will initiate pathways leading to caspase activation and apoptosis directly [55]. Asahi and his team [2] successfully proved that mouse nonparenchymal hepatocytes treated with 100 μM BPA significantly induced endoplasmic reticulum stress-associated apoptosis in vitro (Table 3). This effect is strongly correlated with endoplasmic reticulum stress biomarkers, such as elevation in the expression of CHOP mRNA, caspase-12, and GRP78/Bip [2]. A morphological examination has also shown significant elongation of the rough endoplasmic reticulum, corroborating the endoplasmic reticulum stress diagnosis [2]. More recently, Figueiredo et al. first showed that BPA exposure in mice causes endoplasmic reticulum stress in the liver in vivo [56]. Taken together, BPA-induced hepatocellular injury or apoptosis is associated with endoplasmic reticulum stress.

4.4. Inflammatory Injury. BPA has also been found to be involved in triggering an inflammatory reaction by stimulating the overexpression of a variety of inflammatory-related transcription factor genes and inflammatory-related cytokine genes. Nitric oxide (NO) is a signalling molecule that plays an important role in a wide range of physiological processes, including inflammatory responses. Under normal physiological circumstances, it has an anti-inflammatory influence [57, 58]. NO, on the other hand, is a proinflammatory mediator that, in abnormal conditions, causes inflammation due to excessive production [59, 60]. Regarding the role of NO, there is no definitive reason for NO’s position in pro- or antipathophysiologic situations. However, the amount of NO development in the microenvironment may be a deciding factor [61]. According to Byun et al., NO production is altered by the treatment of BPA in vitro and in vivo [62]. They found
that, regardless of the dosage, the amount of NO released by peritoneal macrophages from BPA-exposed mice was reduced, but only the 500 mg/kg b.w./day group showed a significant reduction [62]. Byun and his team suggested that BPA exposure in humans, whether in the atmosphere or occupational settings, can increase susceptibility to microbial infections or carcinogenesis due to BPA-induced modulation of NO production [62]. Furthermore, they also demonstrated that the level of TNF-α was significantly suppressed with 10 and 100 μM BPA, compared to that of control mice [62]. TNF-α is a pleiotropic and potent proinflammatory cytokine that is involved in inflammation, cell growth, differentiation, and apoptosis in the immune system [63]. The reduction of the TNF-α production could be associated with the downregulation of NO production. Although TNF-α involves mainly inflammation, it is still needed for effective pathogen defence, inflammation resolution, and tissue repair [64]. The homeostatic effect of TNF-α and BPA-induced suppression of TNF-α production could lead to other pathological conditions.

Male rats administrated with BPA at 50 mg/kg b.w./day, orally for eight weeks, significantly increased in proinflammatory cytokines (IL-1β) and at the same time reduced the production of anti-inflammatory/antifibrotic cytokine (IL-10) [23] (Table 3). IL-1β is secreted from hepatic macrophages in various murine models of liver inflammation [65]. The release of IL-1β will further activate macrophages, stimulate the production of other cytokines, and recruit inflammatory cells during infection, injury, and inflammation [66]. Numerous studies have shown that an elevated level of IL-1β is closely associated with liver injury, and its suppression might result in hepatoprotective effects during inflammation [67, 68]. On the other hand, IL-10 is an anti-inflammatory cytokine and critical immunoregulatory molecule that keeps the immune system in check, enabling inflammation to be cleared, thus causing the least amount of harm to the host. It is reported that IL-10 is upregulated during macrophage activation in liver injury and thus has a therapeutic role in the downregulation of inflammation in vivo [23]. A study by Moon and his team also demonstrated that BPA-induced liver injuries were associated with the production of inflammatory cytokines in the liver [21]. They measured the hepatic expression of IL-6 and TNF-α at 1, 6, and 24 hr after the injection of 1.2 mg/kg b.w./day of BPA in animals. The results show that the levels of IL-6 and TNF-α were increased in the BPA-treated group compared to the control. Wang’s laboratory also demonstrated similar results as in Moon’s laboratory, where the serum levels of IL-1β, IL-6, IL-8, and TNF-α in the BPA group were markedly higher than those in the control group [48]. Collectively, BPA is capable of inducing a liver inflammatory response by upregulating pro-inflammatory cytokines, while at the same time downregulating anti-inflammatory cytokines, which in turn leads to liver injury and damage.

5. Conclusion and Future Perspective

Extensive scientific research has documented the side effects of BPA on human health, which include affecting neuronal development, reproductive system, endocrine system, metabolism, cardiovascular system, immunological diseases, and even cancer. However, according to the European Food Safety Authority (EFSA), many factors render it difficult to conclude that BPA is harmful to human health, including toxicokinetic variations between animal and human models, various checked routes of exposure, and the nonreproducibility of human experiments on larger scales [69]. Despite these variables, a recent meta-analysis reported a relationship between early BPA exposure and hyperactivity in children. Thus, understanding how BPA works and causes alterations in organs, especially liver injury or damage, can aid in the prevention and diagnosis of the resulting health problems (Figure 1), as well as the development of more effective approaches and technologies for treating BPA-related liver pathological conditions. It is essential to further analyse liver pathologies in rodents and higher mammals with early life BPA exposure at relevant doses and to evaluate whether these pathological changes could trigger or promote cancer formation when coupled with additional carcinogenic insults. Furthermore, it is strongly recommended that the regulation of BPA usage should be revisited to protect human health.

Data Availability

The datasets supporting the conclusions of this study are included within the manuscript.

Conflicts of Interest

The authors declare that there is no conflict of interest.

Acknowledgments

This research was funded by the Long Term Research Grant Scheme-Malaysia Research University Network (Grant No. 6300218-14001). The authors would like to thank all research universities in Malaysia, especially Universiti Malaya, which approved this project.

References

[1] S. S. Andra, P. Charisiadis, M. Arora, J. V. van Vliet-Ostapchouk, and K. C. Makris, “Biomonitoring of human exposures to chlorinated derivatives and structural analogs of bisphenol A,” Environment international, vol. 85, pp. 352–379, 2015.

[2] J. Asahi, H. Kamo, R. Baba et al., “Bisphenol A induces endoplasmic reticulum stress-associated apoptosis in mouse non-parenchymal hepatocytes,” Life Sciences, vol. 87, no. 13-14, pp. 431–438, 2010.
M. Ashfaq, Q. Sun, H. Zhang et al., “Occurrence and fate of bisphenol A transformation products, bisphenol A mono-methyl ether and bisphenol A dimethyl ether, in wastewater treatment plants and surface water,” *Journal of Hazardous Materials*, vol. 357, pp. 401–407, 2018.

K. Becker, T. Güen, M. Seiwert et al., “GerES IV: phthalate metabolites and bisphenol A in urine of German children,” *International Journal of Hygiene and Environmental Health*, vol. 212, no. 6, pp. 685–692, 2009.

T. Bushnik, D. Haines, P. Levallois, J. Levesque, J. Van Oostdam, and C. Vial, “Lead and bisphenol A concentrations in the Canadian population,” *Health Reports*, vol. 21, no. 3, 2010.

A. Calafat, Z. Kuklenyik, J. A. Reidy, S. P. Caudill, J. Ekon, and L. L. Needham, “Urineary concentrations of bisphenol A and 4-nonylphenol in a human reference population,” *Environmental Health Perspectives*, vol. 113, no. 4, pp. 391–395, 2005.

A. Calafat, X. Ye, L. Y. Wong, J. A. Reidy, and L. L. Needham, “Exposure of the U.S. population to Bisphenol A and 4-tertiary-octylphenol: 2003–2004,” *Environmental Health Perspectives*, vol. 116, no. 1, pp. 39–44, 2008.

W. Dekant and W. Völkel, “Human exposure to bisphenol A by biomonitoring: methods, results and assessment of environmental exposures,” *Toxicology and Applied Pharmacology*, vol. 228, no. 1, pp. 114–134, 2008.

Y. Lin, X. Sun, L. Qiu et al., “Exposure to bisphenol A induces dysfunction of insulin secretion and apoptosis through the damage of mitochondria in rat insulinoma (INS-1) cells,” *Cell Death & Disease*, vol. 4, no. 1, article e460, 2013.

H. Mielke and U. Gundert-Remy, “Bisphenol A levels in blood depend on age and exposure,” *Toxicology Letters*, vol. 190, no. 1, pp. 32–40, 2009.

L. N. Vandenberg, R. Hauser, M. Marcus, N. Olea, and W. V. Welschons, “Human exposure to bisphenol A (BPA),” *Reproductive Toxicology*, vol. 24, no. 2, pp. 139–177, 2007.

Y. Kanno, H. Okada, T. Kobayashi, T. Takenaka, and H. Suzuki, “Effects of endocrine disrupting substance on estrogen receptor gene transcription in dialysis patients,” *Therapeutic Apheresis and Dialysis*, vol. 11, no. 4, pp. 262–265, 2007.

K. Murakami, A. Ohashi, H. Hori et al., “Accumulation of bisphenol A in hemodialysis patients,” *Blood Purification*, vol. 25, no. 3, pp. 290–294, 2007.

G. Ginsberg and D. C. Rice, “Does rapid metabolism ensure negligible risk from bisphenol A?,” *Environmental Health Perspectives*, vol. 117, no. 11, pp. 1639–1643, 2009.

G. Csanády, H. Oberste-Frielinghaus, B. Semder, C. Baur, K. T. Schneider, and J. G. Filser, “Distribution and unspecific protein binding of the xenoreotoxins bisphenol A and daidzein,” *Archives of Toxicology*, vol. 76, no. 5–6, pp. 299–305, 2002.

Z. H. Ke, J. X. Pan, L. Y. Jin et al., “Bisphenol A exposure may induce hepatic lipid accumulation via reprogramming the DNA methylation patterns of genes involved in lipid metabolism,” *Scientific Reports*, vol. 6, no. 1, 2016.

A. Korkmaz, M. A. Ahbab, D. Kolankaya, and N. Barlas, “Influence of vitamin C on bisphenol A, nonylphenol and octylphenol induced oxidative damages in liver of male rats,” *Food and Chemical Toxicology*, vol. 48, no. 10, pp. 2865–2871, 2010.

D. Aniel, S. P. Ratt, M. Arshall, and M. K. Aplan, “Evaluation of abnormal liver enzyme results in asymptomatic patients,” *New England Journal of Medicine*, vol. 342, no. 17, pp. 1266–1271, 2000.
rats,” *Biochemical and Biophysical Research Communications*, vol. 494, no. 1-2, pp. 107–112, 2017.

[33] W. Xia, Y. Jiang, Y. Li et al., “Early-life exposure to bisphenol A induces liver injury in rats involving mitochondria-mediated apoptosis,” *PLoS One*, vol. 9, no. 2, article e90443, 2014.

[34] M. Zaulet, S. E. M. Kevorkian, S. Dinescu et al., “Protective effects of silymarin against bisphenol A-induced hepatotoxicity in mouse liver,” *Experimental and Therapeutic Medicine*, vol. 13, no. 3, pp. 821–828, 2017.

[35] M. Uzunhisarcıklı and A. Aslanturk, “Hepatoprotective effects of curcumin and taurine against bisphenol A-induced liver injury in rats,” *Environmental Science and Pollution Research*, vol. 26, no. 36, pp. 37242–37253, 2019.

[36] N. C. Akçay, S. Ömeroğlu, S. Ö. A. Dizakar et al., “The effects of melatonin on possible damage that will occur on adipocytes and liver tissue by coadministration of fructose and bisphenol a (BPA),” *Environmental Science and Pollution Research*, vol. 27, no. 14, pp. 16231–16245, 2020.

[37] S. S. M. Zaid, S. N. H. Rohim, G. Y. Meng, and N. M. Mustapha, “Post-weaning exposure to bisphenol A induces histological changes in the liver,” *Pertanika Journal of Science and Technology*, vol. 27, no. 2, 2019.

[38] Z. Long, J. Fan, G. Wu et al., “Gestational bisphenol A exposure induces fatty liver development in male offspring mice through the inhibition of HNF1b and upregulation of PPARy,” *Cell Biology and Toxicology*, vol. 37, no. 1, pp. 65–84, 2021.

[39] F. Magnani and A. Mattevi, “Structure and mechanisms of ROS generation by NADPH oxidases,” *Current Opinion in Structural Biology*, vol. 59, pp. 91–97, 2019.

[40] Z. Liu and X. Qu, “New insights into nanomaterials combating bacteria: ROS and beyond,” *Science China Life Sciences*, vol. 62, no. 1, pp. 150–152, 2019.

[41] R. L. Auten and J. M. Davis, “Oxygen toxicity and reactive oxygen species: the devil is in the details,” *Pediatric Research*, vol. 66, no. 2, pp. 121–127, 2009.

[42] A. Kourouma, C. Quan, P. Duan et al., “Bisphenol A induces apoptosis in liver cells through induction of ROS,” *Advances in Toxicology*, vol. 2015, Article ID 901983, 10 pages, 2015.

[43] E. Rencizügullari and M. Aydin, “Genotoxic and mutagenic studies of teratogens in developing rat and mouse,” *Drug and Chemical Toxicology*, vol. 42, no. 4, pp. 409–429, 2019.

[44] D. Degli Esposti, J. Hamelin, N. Bosselut et al., “Mitochondrial roles and cytoprotection in chronic liver injury,” *Biochemistry Research International*, vol. 2012, 16 pages, 2012.

[45] R. Dua, A. Sunkaria, V. Kumar, and K. D. Gill, “Impaired mitochondrial energy metabolism and kinetic properties of cytochrome oxidase following acute aluminium phosphate exposure in rat liver,” *Food and Chemical Toxicology*, vol. 48, no. 1, pp. 53–60, 2010.

[46] Y. Jiang, X. Zhou, X. Chen et al., “Benzo(a)pyrene-induced mitochondrial dysfunction and cell death in p53-null Hep3B cells,” *Mutation Research – Genetic Toxicology and Environmental Mutagenesis*, vol. 726, no. 1, pp. 75–83, 2011.

[47] S. Khan, S. Beigh, B. P. Chaudhari et al., “Mitochondrial dysfunction induced by Bisphenol A is a factor of its hepatotoxicity in rats,” *Environmental Toxicology*, vol. 31, no. 12, pp. 1922–1934, 2016.

[48] K. Wang, Z. Zhao, and W. Ji, “Bisphenol A induces apoptosis, oxidative stress and inflammatory response in colon and liver of mice in a mitochondria-dependent manner,” *Biomedicine and Pharmacotherapy*, vol. 117, article 109182, 2019.

[49] K. R. Bhattarai, T. A. Riaz, H. R. Kim, and H. J. Chae, “The aftermath of the interplay between the endoplasmic reticulum stress response and redox signaling,” *Experimental and Molecular Medicine*, vol. 53, no. 2, pp. 151–167, 2021.

[50] J. Hitomi, T. Katayama, M. Taniguchi, A. Honda, K. Imamizu, and M. Toyohama, “Apoptosis induced by endoplasmic reticulum stress depends on activation of caspase-3 via caspase-12,” *Neuroscience Letters*, vol. 357, no. 2, pp. 127–130, 2004.

[51] I. Tabas and D. Ron, “Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress,” *Nature Cell Biology*, vol. 13, no. 3, pp. 184–190, 2011.

[52] M. Yan, S. Shu, C. Guo, C. Tang, and Z. Dong, “Endoplasmic reticulum stress in ischemic and nephrotic acute kidney injury,” *Annals of Medicine*, vol. 50, no. 5, pp. 381–390, 2018.

[53] J. D. Malhotra and R. J. Kaufman, “The endoplasmic reticulum and the unfolded protein response,” *Seminars in Cell and Developmental Biology*, vol. 18, no. 6, pp. 716–731, 2007.

[54] R. Iurlaro and C. Muñoz-Pinedo, “Cell death induced by endoplasmic reticulum stress,” *FEBS Journal*, vol. 283, no. 14, pp. 2640–2652, 2016.

[55] D. G. Breckenridge, M. Germain, J. P. Mathai, M. Nguyen, and G. C. Shore, “Regulation of apoptosis by endoplasmic reticulum pathways,” *Oncogene*, vol. 22, no. 53, pp. 8608–8618, 2003.

[56] L. S. Figueiredo, K. M. Oliveira, I. N. Freitas et al., “Bisphenol-A exposure worsens hepatic steatosis in ovariectomized mice fed on a high-fat diet: role of endoplasmic reticulum stress and fibrogenic pathways,” *Life Sciences*, vol. 256, article 118012, 2020.

[57] B. B. Mishra, R. R. Lovellwell, A. J. Olive et al., “Nitric oxide prevents a pathogen- permissive granulocytic inflammation during tuberculosis,” *Nature Microbiology*, vol. 2, no. 7, article 17072, 2017.

[58] S. Varga, L. Juhász, P. Gál et al., “Neuronal nitric oxide mediates the anti-inflammatory effects of intestinal ischemic preconditioning,” *Journal of Surgical Research*, vol. 244, pp. 241–250, 2019.

[59] S. Papi, F. Ahmadizad, and A. Hasanvand, “The role of nitric oxide in inflammation and oxidative stress,” *Immunopathologica Persa*, vol. 5, no. 1, 2019.

[60] J. N. Sharma, A. Al-Omran, and S. S. Parvathy, “Role of nitric oxide in inflammatory diseases,” *Inflammopharmacology*, vol. 15, no. 6, pp. 252–259, 2007.

[61] H.-T. Chung, H.-O. Pae, B.-M. Choi, T. R. Billiar, and Y.-M. Kim, “Nitric oxide as a bioregulator of apoptosis,” *Biochemical and Biophysical Research Communications*, vol. 282, no. 5, pp. 1075–1079, 2001.

[62] J. A. Byun, Y. Heo, Y. O. Kim, and M. Y. Pyo, “Bisphenol A-induced downregulation of murine macrophage activities in vitro and ex vivo,” *Environmental Toxicology and Pharmacology*, vol. 19, no. 1, pp. 19–24, 2005.

[63] H. H. Zelová and J. Hořák, “TNF-α signalling and inflammation: interactions between old acquaintances,” *Inflammation Research*, vol. 62, no. 7, pp. 641–651, 2013.

[64] G. D. Kalliolias and L. B. Ivashkiv, “TNF biology, pathogenic mechanisms and emerging therapeutic strategies,” *Nature Reviews Rheumatology*, vol. 12, no. 1, pp. 49–62, 2016.

[65] H. W. Zimmermann, C. Trautwein, and F. Tacke, “Functional role of monocytes and macrophages for the inflammatory response in colon and liver,” *World Journal of Gastroenterology*, vol. 22, no. 15, pp. 3631–3638, 2016.
response in acute liver injury,” *Frontiers in Physiology*, vol. 3, 2012.

[66] Y. C. Li, Y. H. Kuan, F. M. Huang, and Y. C. Chang, “The role of DNA damage and caspase activation in cytotoxicity and genotoxicity of macrophages induced by bisphenol-A-glycidyldimethacrylate,” *International Endodontic Journal*, vol. 45, no. 6, pp. 499–507, 2012.

[67] N. Milošević, M. Rütter, Y. Ventura, Y. Kezerle, V. Feinshtein, and A. David, “Attenuation of neutrophil-mediated liver injury in mice by drug-free E-selectin binding polymer,” *Journal of Controlled Release*, vol. 319, pp. 475–486, 2020.

[68] H. Toughan, S. R. Khalil, A. A. El-Ghoneimy, A. Awad, and A. S. Seddek, “Effect of dietary supplementation with Spirulina platensis on Atrazine-induced oxidative stress-mediated hepatic damage and inflammation in the common carp (*Cyprinus carpio* L.),” *Ecotoxicology and Environmental Safety*, vol. 149, pp. 135–142, 2018.

[69] S. Almeida, A. Raposo, M. Almeida-González, and C. Carrascosa, “Bisphenol A: food exposure and impact on human health,” *Comprehensive Reviews in Food Science and Food Safety*, vol. 17, no. 6, pp. 1503–1517, 2018.