Reviews of Environmental Contamination and Toxicology (2022) 260:10
https://doi.org/10.1007/s44169-022-00011-z

REVIEW

Impact of Bisphenol A on Structure and Function of Mitochondria: A Critical Review

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Received: 29 November 2021 / Accepted: 26 October 2022 / Published online: 9 November 2022

Abstract

Bisphenol A (BPA) is an industrial chemical used extensively to manufacture polycarbonate plastics and epoxy resins. Because of its estrogen-mimicking properties, BPA acts as an endocrine-disrupting chemical. It has gained attention due to its high chances of daily and constant human exposure, bioaccumulation, and the ability to cause cellular toxicities and diseases at extremely low doses. Several elegant studies have shown that BPA can exert cellular toxicities by interfering with the structure and function of mitochondria, leading to mitochondrial dysfunction. Exposure to BPA results in oxidative stress and alterations in mitochondrial DNA (mtDNA), mitochondrial biogenesis, bioenergetics, mitochondrial membrane potential (MMP) decline, mitophagy, and apoptosis. Accumulation of reactive oxygen species (ROS) in conjunction with oxidative damage may be responsible for causing BPA-mediated cellular toxicity. Thus, several reports have suggested using antioxidant treatment to mitigate the toxicological effects of BPA. The present literature review emphasizes the adverse effects of BPA on mitochondria, with a comprehensive note on the molecular aspects of the structural and functional alterations in mitochondria in response to BPA exposure. The review also confers the possible approaches to alleviate BPA-mediated oxidative damage and the existing knowledge gaps in this emerging area of research.

Introduction

Bisphenol A or BPA [2,2-bis(4-hydroxyphenyl) propane] is a colorless solid, carbon-based synthetic monomer, and a highly used industrial chemical with widespread applications (Nachman et al. 2014; Song et al. 2015; Guo et al. 2017). It is one of the large-scale manufactured industrial chemicals (more than 2.72×10^9 kg/year) commonly used as a plasticizer, monomer, and additive in synthesizing epoxy resins, polycarbonate plastics, and polyvinyl chloride (Khan et al. 2016; Gassman 2017; Urriola-Muñoz et al. 2018). BPA is widely present in food and water containers, air, dust, dental sealants, paints, electronic equipment, toys, cosmetics, car tires, car equipment, flame retardants, inhalers, catheters, and other medical devices (Liao et al. 2012; Khan et al. 2016; Ribeiro et al. 2017; Prins et al. 2018; Shafei et al. 2018). Ingestion, inhalation, and transdermal routes are the frequent modes of BPA exposure in humans (Rubin 2011; Wang et al. 2017; Nomiri et al. 2019). The most common route of BPA's entry into the human system is through consuming water, food, and beverages contaminated with BPA (Agarwal et al. 2016; Begum et al. 2020;

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Adiga et al. 2022). Thermal printed paper can also expose users to BPA transdermally (Bernier and Vandenberg 2017; Almeida et al. 2018). BPA exposure during pregnancy and lactation increased anxiety and depression-like behavior in rodent models (Xu et al. 2012).

The digestive tract primarily absorbs BPA; hence, milk, urine, serum, and fat show a plasma level of BPA ranging from 0.2 to 20 ng/mL. Routine exposure to BPA can result in its accumulation in the body tissues (Andra et al. 2016; Jalal et al. 2018) (Fig. 1). A study has shown the elevation in colonic permeability by dietary BPA (Feng et al. 2019). Dietary BPA deregulated the functions of physical and biological barriers and intestinal chemistry (Feng et al. 2019). Metabolism of BPA occurs in the liver. Once absorbed, the unconjugated BPA is bio-transformed into BPA-glucuronide and BPA-sulfate with the help of the enzymes uridine 5′-diphospho-glucuronyl transferase (UGT) and sulfotransferases (Nachman et al. 2014). BPA is excreted through the urine after detoxification and has a 2-h half-life in blood (Neri et al. 2015). Other routes of BPA elimination include sweat, feces, and bile (Genuis et al. 2012) (Fig. 1). BPA is a well-known, potent endocrine-disrupting chemical that mimics 17β-estradiol and interrupts the normal endocrine signaling processes (Ribeiro et al. 2017; Nomiri et al. 2019). It can bind to the classical nuclear estrogen receptor α (ERα) and estrogen receptor β (ERβ), membrane-associated protein receptor G protein-coupled receptor (GPR30), as well as estrogen receptor γ (ERγ), thus activating the non-classical ER pathways (Carchia et al. 2015; Seachrist et al. 2016; Valentino et al. 2016; Gassman 2017). It competes with 17β estradiol and binds to the estrogen receptor, which triggers endocrine receptor signaling pathways and disrupts normal physiological processes even at low doses (Konieczna et al. 2015; Gao et al. 2015; Gassman 2017; Khan et al. 2021).

BPA exposure contributes to many ailments below the oral reference dose (ORD) established by the United States Environmental Protection Agency (USEPA). USEPA has set 50 µg BPA/kg body weight (kg bw) as the human reference dose (USEPA 2012). The European Food Safety Authority (EFSA) established the temporary Tolerable Daily Intake (t-TDI) of 4 µg/kg body weight/day in 2015 (EFSA 2015). BPA plays a critical role in precocious puberty, polycystic ovary syndrome, female and male infertility, cardiovascular diseases, neurological disorders, and various types of cancer due to its wide-ranging toxic effects (Rutkowska and Rachoń 2014; Inadera 2015; Chen et al. 2018; Matuszczak et al. 2019; Moon et al. 2021; Khan et al. 2021). National Center for Toxicological Research (NCTR) of the US Food and Drug Administration (FDA), the National Toxicology Program (NTP), and the National Institute for Environmental Health Sciences (NIEHS) have performed Consortium Linking Academic and Regulatory Insights on Toxicity of BPA (CLARITY-BPA) study using Sprague–Dawley rats (Heindel et al. 2015). The CLARITY-BPA study was

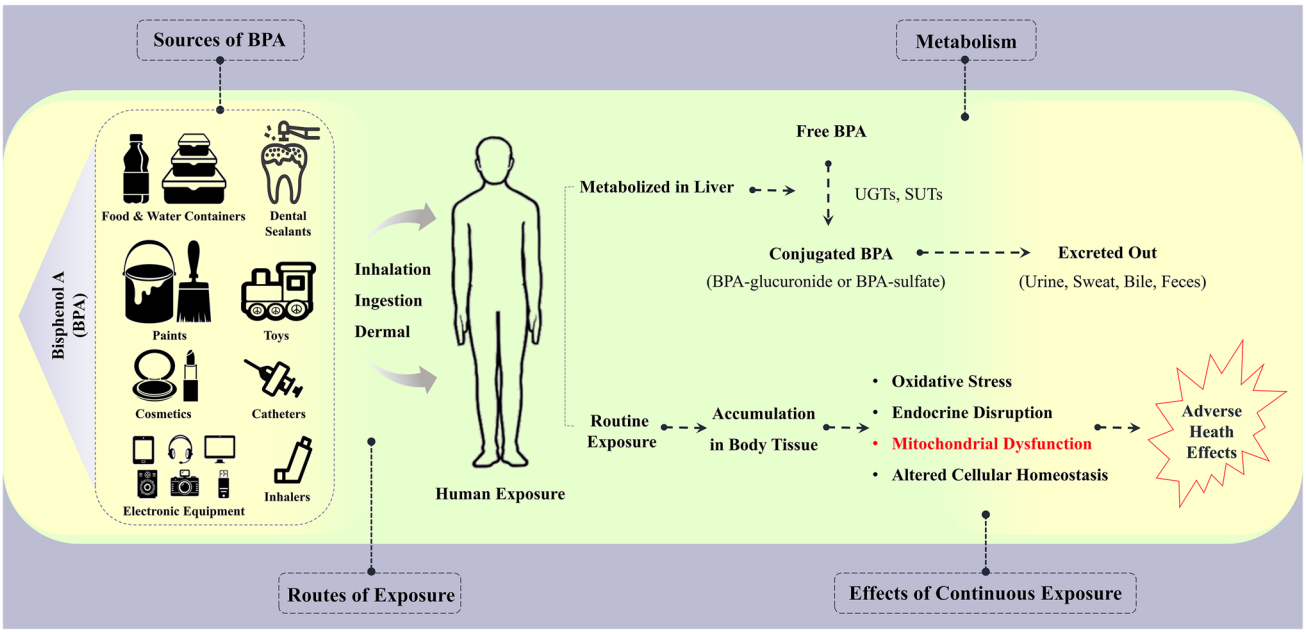

Fig. 1 Bisphenol A (BPA) can enter the human body as leachates from consumer products such as food and water containers, paints, dental sealants, cosmetics, toys, and medical and electronic devices. Free BPA will be bio-transformed upon absorption into BPA-glucuronide or BPA-sulfate, followed by its clearance through urine, sweat, bile, or feces. Routine exposure can accumulate BPA in body tissue, leading to oxidative stress, endocrine disruption, mitochondrial dysfunction, and altered cellular homeostasis. The present review focuses on the alterations in mitochondrial functionalities in response to BPA exposure

carried out following good laboratory practice (GLP) to gain a more comprehensive understanding of the toxicological effects of BPA. Camacho and his group did not observe BPA-associated health effects in treated rats (Camacho et al. 2019). However, exposure to 25,000 µg BPA/kg bw/day was associated with a high occurrence of lesions in the male pituitary and female reproductive tract. Another CLARITY-BPA study has analyzed the effect of BPA exposure on immune cells. However, chronic BPA exposure did not induce substantial change in the composition of immune cells (Li et al. 2018). Prins and co-workers have proposed the increased risk of prostate cancer in rats exposed to BPA (Prins et al. 2018). Another study has proposed the adverse effects of BPA on organ functioning (Heindel et al. 2020). BPA-mediated epigenetic alterations were observed in the hippocampus and hypothalamus of treated rats. A consortium study has reported mammary carcinoma development and a considerable increase in the follicular cysts in female rats treated with BPA (Prins et al. 2019). Collectively, these CLARITY-BPA studies suggest the possible health effects of BPA. Similar detailed investigations are necessary to clarify the ambiguity regarding the harmful effects of BPA on human health.

BPA has gained attention due to its high chances of human exposure and its ability to predispose individuals to adverse health outcomes even at extremely low doses (Rachoń 2015). BPA has been identified as a Group 2A agent by the International Agency for Research on Cancer (IARC) due to its classification as a probable carcinogen and potential tumor-promoting characteristics (Seachrist et al. 2016). Both experimental and epidemiological findings have shown the association of BPA with different human ailments, such as developmental, metabolic, cardiovascular, neurological, respiratory, renal, and reproductive complications (Rochester 2013; Adiga et al. 2022). BPA induces genetic and epigenetic modifications, endocrine disruption, oxidative stress, and mitochondrial dysfunctions and interferes with the cellular signaling cascades (Rezg et al. 2014). Growing evidence illustrates that BPA induces oxidative stress by targeting the mitochondria's structure, function, and signaling aspects (Marroqui et al. 2018; Wang et al. 2019b).

Mitochondria are structurally complex, versatile organelles in the cytoplasm and occupy a canonical role as the cell's energy source (Hsu et al. 2016). Known to operate as power generators by synthesizing adenosine triphosphate (ATP), mitochondria play a central role in fuelling normal metabolic functions (Hertweck and Dasgupta 2017). In addition to its role in cellular bioenergetics, mitochondria modulate many other biological processes such as reactive oxygen species (ROS) generation, calcium (Ca^{2+}) homeostasis, cell growth, fatty acid metabolism, amino acid metabolism, and regulation of cell death (Choudhury and Singh 2017). It uses Ca^{2+} for modulating cell signaling pathways associated with cell proliferation, differentiation, cell cycle progression, and apoptosis (Osellame et al. 2012). Metabolic alterations in mitochondria contribute to various chronic health disorders such as cardiovascular disorders, autism, muscular dystrophy, diabetes, and different types of cancer (Bravo-Sagua et al. 2017). Several environmental agents, including BPA, exert lethal effects by targeting mitochondria (Meyer et al. 2013; Meli et al. 2020). Owing to its ability to interfere with energy homeostasis, BPA is also considered a metabolism-disrupting chemical (MDC) (Marraudino et al. 2019).

Previous reports demonstrate the adverse effects of BPA on mitochondrial functionalities. However, to the best of our knowledge, a comprehensive review describing the impact of BPA on mitochondria is lacking. In this regard, the present review emphasizes the emerging role of BPA in altering mitochondrial functionalities, associated mechanisms, and the resulting complications (Fig. 2). Moreover, the review also provides data on in-vitro and in-vivo models, doses tested, experimental design, and toxicological impact and confers research gaps and recommendations for future investigations.

Effects of BPA Relative to Mitochondria

Accumulating evidence suggests BPA is an evolving menace to mitochondrial functions (Moon et al. 2012; Wang et al. 2019b, 2021). The subsequent sections illustrate the role of BPA in modulating oxidative stress, mitochondrial membrane potential (MMP), mitochondrial Ca^{2+}, mitochondrial DNA (mtDNA) damage, mitochondrial biogenesis, dynamics, apoptosis, mitophagy, bioenergetics, and respiration.

Oxidative Stress

ROS are produced primarily in mitochondria as a result of electron leak from the electron transport chain (ETC) during oxidative phosphorylation (OXPHOS) (Liou and Storz 2010; Zorov et al. 2014). The cell generates ROS such as superoxide anions, hydroxyl radicals, and peroxides as a part of normal cellular metabolism. The ability of the cell to maintain the redox balance plays a crucial role in all aspects of growth, survival, and development and regulates the cell's response to endogenous and exogenous stimuli (Ursini et al. 2016). An increase in ROS level damages mitochondrial structure and function and alters mitochondrial signaling (Bhatti et al. 2017). It also reduces MMP and alters the permeability transition of the mitochondrial membrane (Pfeifer et al. 2015). Cells have adapted to highly regulated pathways involving antioxidant defense systems to maintain a redox equilibrium and prevent the deleterious effect caused by ROS accumulation (Gassman 2017).

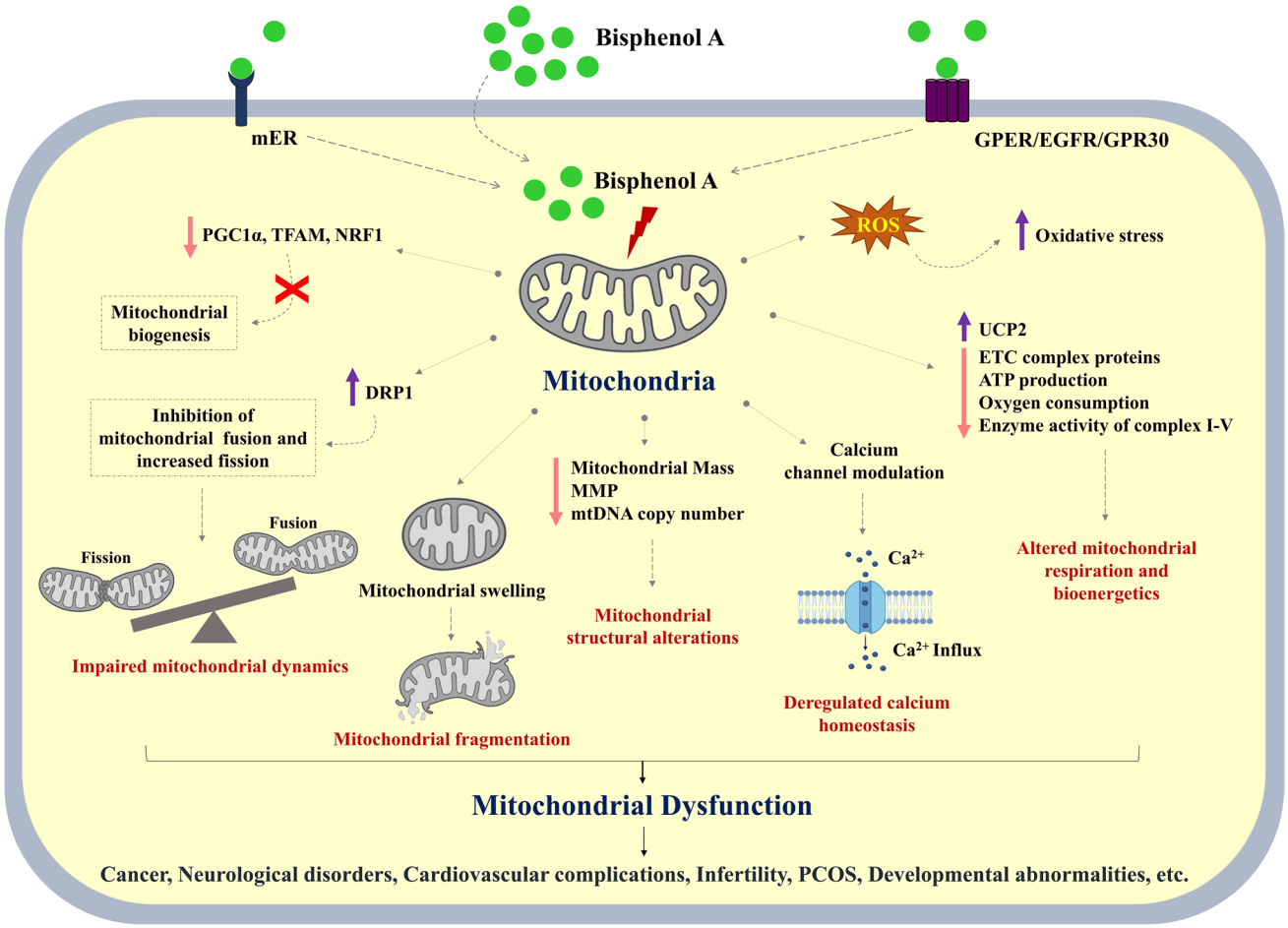

Fig. 2 BPA-induced mitochondrial toxicity. BPA targets mitochondria to induce various toxic effects. BPA affects mitochondria's structure and function, leading to compromised mitochondrial functionalities and facilitating pathophysiological aspects of numerous diseases and disorders

The BPA-mediated neurotoxic effect involves the activation of the oxidative stress pathway. A recent study using HT-22 cells showed that BPS, BPA, and BPB were toxic to hippocampal neuronal cells (Pang et al. 2019). The same study also showed that 6-h of bisphenol exposure led to a significant increase in ROS. Besides this, upon 24 and 48 h of exposure, higher apoptosis induction was observed, and 7 days of exposure inhibited cell proliferation. Thus, it is evident that long-term exposure to bisphenols may bring in cell cycle arrest and cell death. Similarly, primary hippocampal neurons exposed to bisphenols showed increased ROS and oxidative damage (Meng et al. 2021). The study also showed that hippocampal neurons isolated from males were more sensitive to bisphenols than females (Meng et al. 2021).

BPA administration is known to cause cytotoxicity in various cell and tissue types via oxidative stress and mitochondrial dysfunction (Table 1). BPA exposure affects early embryonic development in the porcine study model (Choi et al. 2016; Guo et al. 2017). Oxidative stress-induced mitochondrial damage leads to the mitochondrial release of cytochrome c (Cyt-C), while DNA damage results in the inactivation of the p53–p21 pathway (Guo et al. 2017). Several researchers have specifically investigated the ROS and antioxidant levels upon BPA exposure. Both low- and high-dose BPA exposure induced ROS generation in in-vitro cell culture systems (Ooe et al. 2005; Huc et al. 2012; Meli et al. 2020). Interestingly, the superoxides produced in response to BPA contributed to the total ROS level and lipid peroxidation in HepG2 cells (Huc et al. 2012). BPA increased the oxidative stress and inflammatory response in human endometrial stromal cells via the Mitogen-activated protein kinase/protein kinase B/nuclear factor-kappa (ERK/AKT/NF-κB) axis (Cho et al. 2018). An inverse correlation between ROS and antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT) was reported (Ighodaro and Akinloye 2018). This implied that BPA-mediated elevation in ROS level was due to the reduced expression of antioxidant enzymes. Reports have shown the ability of BPA to induce nitric oxide via upregulation of nitric oxide synthase (Chouhan et al. 2015; Wang et al. 2019a). In the hearts of

Table 1 Association between BPA and oxidative stress in mitochondria

Study model and dosage used	Target	References
LAPC-4 and PC-3 cells (0.67 pM to 0.67 μM BPA for 1 h)	Increases ROS and causes oxidative stress	Koong and Watson (2015)
HepG2 cells (1 pM, and 0.67 mM BPA for 24, 48 and 72 h)	Increases mitochondrial ROS, IL8 and TNFα secretion, generates mitochondria-dependent superoxide anion, disturbs mitochondrial homeostasis, triggers lipogenesis, and mobilizes inflammatory cells	Huc et al. (2012)
Pancreatic islets of C57/B6 male mice (1 nM BPA for 48 h)	Enhances intracellular ROS and oxidative stress, affects cellular viability and alters mitochondrial function	Carchia et al. (2015)
FRTL-5 Thyroid cells (1 nM BPA for 1, 3, and 7 days)	Exerts indirect genotoxicity in thyroid cells	Porreca et al. (2016)
184A1 and MCF7 cell lines (10 and 100 nM BPA for 24 h)	Induces ROS production and DNA damage through oxidative stress	Pfeifer et al. (2015)
HepG2 cells (0.1 and 10 μmol/L BPA for 24 h)	Generates reactive quinone metabolites and oxidative stress	Fic et al. (2013)
Mouse Sertoli TM4 cells (0.34 μM, 0.34 mM BPA for 24 h)	Stimulates proliferation of Sertoli TM4 cells, increases ROS, depletes intracellular GSH and mitochondrial density	Ge et al. (2014)
INS-1 pancreas cell line (25, 50, and 100 μM BPA for 24 h)	Increases intracellular ROS and decreases GSH level	Xin et al. (2014)
GT1-7 Hypothalamic neurons (50–100 μM BPA for 6 h)	Generates intracellular peroxide(s), enhances superoxide radicals, and promotes cellular oxidative stress	Babu et al. (2013)
Hippocampal neural stem cells (100 μM BPA for 24 h)	Increases ROS, depletes antioxidants, induces mitochondrial dysfunction, neurotoxicity, and promotes apoptosis	Agarwal et al. (2016)
Mouse Neuro2a (neuronal) and GC1 cells (spermatogonia) (50 and 100 μM BPA for 24 and 48 h)	Generates hROS, causes oxidative stress, stimulates O_2^- production and enhances oxidization of DJ-1	Ooe et al. (2005)
Human colonic goblet cell line (LS174 T) (150 μM/mL BPA for 24 h)	Elevates mitochondrial and intracellular ROS, increases MDA and H_2O_2 levels, and disrupts intestinal epithelial cell function	Zhao et al. (2019)
Mouse embryonic fibroblasts (150 μM BPA for 1 h)	Increases intracellular ROS, 5-OH-Cyt and thymine glycol levels and induces DNA lesions	Gassman et al. (2015)
Human renal proximal tubular epithelial cells (200 μM BPA for 24 h)	Increases ROS, intramitochondrial superoxide anion, mitochondrial depolarization, and induces cell toxicity	Bosch-Panadero et al. (2018)
HCT116 cells (250 μM BPA for 24 h)	Increases intracellular and mitochondrial ROS, increases MDA and H_2O_2, and causes oxidative stress in colonic cells	Qu et al. (2018)
Bone mesenchymal stem cells (hBMSCs) (250 and 500 μM BPA for 18 h)	Induces oxidative stress-mediated cytotoxicity, increases MDA and decreases β-catenin levels, disrupts the transcriptional activity of the β-catenin/LEF complex and programmed celldeath	Leem et al. (2017)
Male Wistar Albino rats (2 and 20 μg/kg bw BPA for 28 days)	Increases MDA levels, decreases GSH levels in brain, induces cognitive dysfunction and oxidative stress	Jain et al. (2011)
Male mice (ICR), (exposed during embryonic/fetal life, 5 or 10 μg/mL BPA for 1 week)	Increases CAT and GPx activity in liver and kidney, increases thiobarbituric acid level in brain, kidney and testis, induces tissue oxidative stress and peroxidation	Kabuto et al. (2004)
Adult rats (10 μg, 5 mg, and 50 mg/kg bw BPA for once a day for 6 days)	Increases lipid peroxidation and decreases GSH, exhibits genotoxicity and oxidative stress	Tiwari et al. (2012)
Erythrocytes (25–150 μg/mL BPA for 4 h)	Destabilizes RBC membrane through ROS production and causes haemolysis	Sangai et al. (2018)
Erythrocytes (25–150 μg/mL BPA for 4 h)	Increases LPO and decreases SOD, CAT, and GPx activity, alters erythrocyte size and RBC haemolysis	Sangai et al. (2018)
Pregnant Wistar rats (40 μg/kg/day BPA for gestational day 0 to postnatal day 21)	Increases ROS and oxidative stress	Jiang et al. (2014a)

Table 1 (continued)

Study model and dosage used	Target	References
Male CD-1 mice (50 µg/kg/day BPA for 10 weeks)	Increases ROS, MDA and H_2O_2 levels, reduces SOD, GSH, CAT and proinflammatory cytokines (IL-1β, -6, -8 and TNF-α), inflammatory response and apoptosis	Wang et al. (2019b)
Male Swiss albino mice (300, 900, and 3000 µg/kg bw/day BPA during the breastfeeding period, 21 days)	Induces testicular oxidative damage, impairs antioxidant capability, DNA integrity, induces testicular degeneration, impairs mitochondrial functionality and sperm parameters	Kalb et al. (2016)
Hepatic mitochondria from Male F344/DuCrj rats (0.25 and 1 mM BPA for 30 min)	Inhibits mitochondrial oxidative phosphorylation, and induces cytotoxicity	Nakagawa and Tayama (2000)
Lymphoblastoid cell lines (25, 50, and 100 mM BPA for overnight)	Increases ROS, induces oxidative stress and cytotoxicity	Kaur et al. (2014)
Male Wistar Albino rats (0.2, 2 and 20 mg/kg bw/day BPA for 30 days)	Decreases SOD, CAT, GSH and GPx, increases H_2O_2 levels and lipid peroxidation in liver mitochondria, and generates free oxygen radicals	Bindhumol et al. (2003)
Male Wistar rats (0.2, 2 and 20 mg/kg BPA for 4 days)	Downregulates SOD, CAT, GSH and GPx, enhances H_2O_2 and lipid peroxidation, decreases epididymal sperm motility and sperm count	Chitra (2003)
Adult male mice (0.5 and 2 mg/kg BPA for 4 weeks)	Increases blood glucose, lipid profile and MDA levels, reduces high-density lipoprotein (HDL) and GSH levels	Moghaddam et al. (2015)
Male Wistar albino rats (0.1, 1, 10, and 50 mg/kg bw BPA for 4 weeks)	Decreases GSH, SOD, GPx, glutathione-*S*-transferase, glutathione reductase and CAT levels and causes hepatotoxicity	Hassan et al. (2012)
C57BL/6 male mice (1.2 mg/kg bw/day BPA for 5 days)	Increases hepatic MDA concentrations, decreases expression of GPx, increases hepatic expression of IL6, increases hepatic oxidative stress and impairs mitochondrial functions	Moon et al. (2012)
Male mice (ICR) (25 and 50 mg/kg/day BPA for 5 days)	Increases SOD activity and decreases CAT level in liver, decreases GPx activity in kidney, increases GSH + GSSG levels in brain, kidney, liver, and testes, and induces toxicity by overproduction of H_2O_2	Kabuto et al. (2003)
Male Wistar rats (25 mg/kg/day BPA for 45 days)	Decreases GSH and enhances LPO and MDA levels, generates ROS and causes oxidative damage in brain	Aydoğan et al. (2008)
Wistar rats (150, 250, and 500 mg/kg bw BPA for 14 days)	Enhances oxidative stress, mitochondrial superoxide generation, reduces glutathione level, and downregulates the activity of SOD and LPO	Khan et al. (2016)
Adult male Sprague–Dawley rats (200 mg/kg bw/day BPA for 10 days)	Increases TBARS levels, decreases SOD activity and causes testicular oxidative stress	Wu et al. (2013)
Male Wistar rats (250 mg/kg BPA for 14 days)	Increases ROS, MMP and MDA production, decreases GSH and CAT, and induces liver mitochondrial damage	Mahdavinia et al. (2019)

CAT catalase; *GPx* glutathione peroxidase; *GSH* reduced glutathione; *HDL* high-density lipoprotein; H_2O_2 hydrogen peroxide; *IL8* interleukin 8; *INS* insulinoma; *LPO* lipid peroxidation; *MDA* malonaldehyde; *MMP* mitochondrial membrane potential; *ROS* reactive oxygen species; *SOD* superoxide dismutase; *TBARS* thiobarbituric acid reactive substances; *GSSG* oxidized glutathione

male rats, BPA reduced catalase activity, glutathione (GSH) levels, and enhanced lipid peroxidation, thus resulting in ROS accumulation and mitochondrial dysfunction (Aboul Ezz et al. 2015). In 2019, Wang et al. investigated the effect of dietary BPA on liver and colon functions. BPA-induced oxidative stress elevated cytokine secretion and lowered antioxidant levels in mice's liver and colon tissue (Wang et al. 2019b). These experimental evidences exemplify the influence of BPA on the antioxidant defense system and the resulting oxidative damage and cellular toxicity.

Mitochondrial Membrane Potential (MMP)

Besides taking part in mitochondrial energetics, MMP participates in several non-energetic functions, such as transporting metal ions to the interior and exporting anions to the exterior of mitochondria (Zorova et al. 2018). The regulation of molecules in and out of mitochondria by MMP is vital for maintaining mitochondrial structure, function, and metabolism. Also, MMP regulates ROS production and removal of defective mitochondria (Zorov et al. 2014). Thus, disturbance in MMP may contribute to numerous pathological conditions. In-vitro and in-vivo investigations have shown that BPA alters MMP to promote mitochondrial dysfunction (Jiang et al. 2015; Kaur et al. 2014; Shirani et al. 2019). BPA exposure below the no observed adverse effect level (NOAEL) (0.05 and 1.2 mg/kg/day for 5 days) led to compromised mitochondrial function, as evidenced by the reduction in MMP, oxygen consumption, and ATP production (Moon et al. 2012). Studies have also reported a significant reduction in the MMP of rat kidney mitochondria exposed to 1–1000 µM of BPA (Kobroob et al. 2018). The decrease in sperm motility accompanied a decrease in MMP upon BPA exposure in chicken (Singh et al. 2015b). BPA (50 µg/kg/day for 10 weeks) facilitated depolarization of MMP, impaired mitochondrial integrity, and resulted in oxidative damage in mice's liver and colon tissues (Wang et al. 2019b). BPA (100 µM) exposure diminished the developmental capacity of mouse oocytes (Pan et al. 2021). The same study also demonstrated the abnormal distribution of mitochondria and decreased MMP upon BPA exposure. BPA-mediated MMP decline may have a decisive role in cellular toxicity. However, the exact molecular mechanism leading to MMP impairment and the consequent effect on mitochondrial function require detailed investigation.

Mitochondrial Calcium

Mitochondria uptake Ca^{2+} through mitochondrial Ca^{2+} uniporter (MCU) and Ca^{2+} level elevation leads to the activation of many enzymes involved in the tricarboxylic acid (TCA) cycle and ATP synthesis (Wacquier et al. 2016). Transfer of Ca^{2+} from the endoplasmic reticulum to mitochondria is indispensable for maintaining cellular energetics, and reduced transfer diminishes OXPHOS activity and energy production (Bustos et al. 2017). Reports have demonstrated that Ca^{2+} uptake by mitochondria depends on MMP, and disruption in uptake may lead to decreased mitochondrial respiration, mitochondrial DNA transcription, mitochondrial biogenesis, cell survival, and apoptosis (Choudhury and Singh 2017). The role of BPA in modulating cellular Ca^{2+} levels is still contentious. Few investigations have shown both the inhibitory and stimulatory effects of BPA on Ca^{2+} influx. A study has reported BPA as a potent Ca^{2+} channel inhibitor and has proposed the involvement of ERβ-dependent pathways in regulating Ca^{2+} entry (Villar-Pazos et al. 2017). A contrasting report has depicted that BPA elevates cytosolic Ca^{2+} by impeding Sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) and stimulating inositol trisphosphate receptor (IP_3R) (Batista-Silva et al. 2020). Using imaging techniques, Derouiche et al. revealed the augmentation of store-operated Ca^{2+} entry in lymph node carcinoma of the prostate (LNCaP) cells treated with BPA (Derouiche et al. 2013). However, reports showing the direct involvement of BPA in regulating mitochondrial Ca^{2+} levels are scarce. Investigations in this aspect may aid in a better understanding of the signaling intricacy associated with the toxicological effects of BPA.

mtDNA Damage

mtDNA damage can result from both exogenous and endogenous agents and the mtDNA repair pathways compensate for the resulting damages (Omar García-Lepe and Ma Bermúdez-Cruz 2019). mtDNA damage is one of the critical factors associated with many mitochondrial disorders (Singh et al. 2015a), including cancer and neurological ailments (Singh et al. 2015b). Oxidative stress is one of the primary causes of mtDNA damage (Cui et al. 2012; Han and Chen 2013). Several findings have depicted the potential of BPA to induce oxidative DNA damage. For instance, BPA affects genomic integrity by impairing chromosome synapsis and disturbing double-strand break repair during meiosis (Allard and Colaiacovo 2010). Gassman et al. have demonstrated the inhibitory effect of BPA on oxidized base lesion DNA repair (Gassman et al. 2015). In ERα negative mammary cells, low-dose BPA exposure resulted in DNA damage by modulating cell cycle regulatory proteins (Pfeifer et al. 2015). Another study has revealed the role of BPA in inducing chromosomal aberrations, which was evident with the presence of pulverized and fragmented chromosomes (Di Pietro et al. 2020). Collectively, these findings strongly suggest the involvement of BPA in causing oxidative DNA damage. Because there have been no reports linking BPA exposure to mtDNA damage, it can be speculated

that similar to that of genomic DNA, BPA exposure may induce oxidative damage in mtDNA. Investigations in this field may shed light on the novel mechanisms of BPA-driven mitochondrial dysfunction.

mtDNA copy number is closely related to cellular health as mutation and mtDNA variations are associated with human diseases such as Parkinson's, Alzheimer's, Huntington's, diabetes, and cancer (Kabekkodu et al. 2014; Li et al. 2019). Several reports have proposed the changes in mtDNA copy number as a potential disease biomarker for cancer (Hu et al. 2016). Furthermore, many environmental agents have caused mitochondrial dysfunction by altering mitochondrial copy numbers. For example, the rat granulosa cells exposed to BPA showed depletion in mtDNA (Lee et al. 2019). Jiang et al. have revealed the role of BPA in altering the mtDNA copy number. They analyzed the induction of oxidative stress, antioxidant status, cytokine levels, and apoptosis in male Wistar rats exposed to BPA. This study has demonstrated the reduced expression of mtDNA encoded genes, reduced mtDNA copy number, and the resulting mitochondrial dysfunction and kidney toxicity in the treated rats (Jiang et al. 2020). Contrastingly, BPA exposure increased mtDNA copy numbers in lymphoblast cells (Kaur et al. 2014). Although BPA affects mtDNA copy number, the exact molecular mechanism is yet to be uncovered.

Mitochondrial Biogenesis and Dynamics

Mitochondrial biogenesis is a highly regulated process in which cells augment mitochondrial mass by fusion and fission (Popov 2020). Physiological conditions such as cell division, differentiation, low temperature, exercise, oxidative stress, and caloric restriction can influence mitochondrial biogenesis (Popov 2020). Proliferator-activated receptor coactivator 1α (*PGC1α*), mitochondrial transcription factor A (*TFAM*), nuclear respiratory factor-1 and -2 (*NRF1* and *NRF2*) also play critical roles in the regulation of mitochondrial biogenesis (Gureev et al. 2019). AMP-activated protein kinase (AMPK) signaling activates *PGC1α* and *NRF-1/2*, leading to the transcription of *TFAM* (Gureev et al. 2019). Following this, TFAM translocates to mitochondria, and by binding to mtDNA, it induces the transcription of genes involved in mitochondrial biogenesis (Gureev et al. 2019). BPA impairs the biogenesis of mitochondria by modifying the expression of associated genes (Lin et al. 2013; Marroqui et al. 2018). Of note, in neonatal rats, prenatal exposure to BPA (50 µg/kg/day) significantly reduced the expression of *PGC1α*, estrogen-related receptor *α* (*ERRα*), *ERRγ*, peroxisome proliferator-activated receptor *α* (*PPARα*), *NRF1*, and *TFAM* (Jiang et al. 2014a). Long-term BPA exposure (50 µg/kg/day for 48 weeks) induced hypermethylation of the *PGC1α* promoter and subsequent downregulation of its expression in the heart tissue of male rats (Jiang et al. 2015). The downregulated genes in response to BPA treatment included *PGC1α*, *NRF1*, *NRF2*, *TFAM*, and their validated target genes such as ATP synthase subunit epsilon (*ATP5E*), ATP synthase subunit O (*ATP5O*), cytochrome b-c1 complex subunit 2 (*UQCRC2*), and *UQCRF1* (Jiang et al. 2015). In zebrafish, BPA exposure affected the expression of critical genes associated with mitochondrial biogenesis and oxidative phosphorylation in male gonads (Chen et al. 2015). The same study has demonstrated reduced sperm quality and count, altered sex ratio, and male-specific reproductive failure in offspring upon BPA exposure.

Both mitochondrial fission and fusion play a key role in mitochondria biogenesis and significantly impact the mitochondrial network. Genes such as dynamin-related protein 1 (*DRP1*), Mitofusin 1 and 2 (*MFN1* and *MFN2*) are known for their involvement in mitochondrial fusion and fission kinetics (Agarwal et al. 2016). A balance between fission and fusion maintains mitochondrial morphology and preserves a healthy pool of mitochondria by actively controlling mitophagy (Vantaggiato et al. 2019). The imbalance in mitochondrial fission is exhibited by well-developed, elongated mitochondria, whereas disparity in mitochondrial fusion results in increased mitochondrial fragmentation (Senft and Ronai 2016). Different disease conditions showed an increase in the expression of DRP1, Optic atrophy-1 (OPA1), MFN1, and MFN2 proteins (Hall et al. 2014; Zorzano and Claret 2015; Liu et al. 2020). Impaired mitochondrial dynamics disrupt the equilibrium between fusion and fission, causing the accumulation of defective mitochondria and resulting in mitochondrial dysfunction (Agarwal et al. 2016; Wang et al. 2017). DRP1 is an extensively studied protein related to BPA exposure and mitochondrial dynamics. Peerapanyasut et al. have reported the upregulation of the active form of DRP1 in the kidney and liver of rats exposed to BPA (50 mg/kg for 5 weeks) (Peerapanyasut et al. 2019). Low-dose BPA exposure upregulated the active form of DRP1 in human embryonic stem cells derived from cardiomyocytes (Cheng et al. 2020). Chronic exposure to BPA led to the upregulation of *DRP1* in hippocampal neural stem cells derived from rat embryos. Also, inhibition of *DRP1* mitigated BPA-induced mitochondrial dysfunction. Thus, targeting *DRP1* can be used to mitigate BPA-induced neurotoxicity and neurodegeneration (Agarwal et al. 2016). BPA exposure led to an increase in the number of fragmented mitochondria with depletion of cristae and significantly altered the structure of mitochondria from elongated and tubular to small and rounded structures (Agarwal et al. 2016). BPA exposure altered mitochondrial biogenesis by hampering the GFER-mediated mitochondrial protein import in the hippocampus of the rat brain (Goyal et al. 2021). The same study demonstrated the accompanying mitochondrial damage, distorted cristae, and reduced localization of GFER to the mitochondrial intermembrane

space in the rat neurons. These observations signify that short-term and long-term exposure to BPA disturbs mitochondrial dynamics by inhibiting mitochondrial biogenesis and modifying fission and fusion kinetics.

Apoptosis

Several previous reports have shown that BPA regulates cell signaling cascades leading to ROS generation and oxidative damage (Gassman 2017). BPA induces apoptosis in various cell and tissue types by targeting the mitochondrial signaling pathways (Fig. 3). BCL2-like protein (BAX) and B cell lymphoma 2 (BCL2) regulate apoptosis by releasing Cyt-C and altering MMP levels. BCL2 and BAX inhibit and promote apoptosis, respectively (Wang et al. 2017). Inappropriate activation or suppression of apoptosis is associated with different pathological conditions, including neurodegenerative diseases, many types of cancer, and autoimmune disorders (Elmore 2007). In INS1 cells, BPA-mediated apoptosis induction involved Cyt-C release and subsequent activation of caspases. Also, these cells displayed mitochondrial toxicity, involving fragmentation of mitochondria, reduction in mitochondrial mass and MMP, and ATP depletion upon BPA exposure (Lin et al. 2013). BPA-induced germ cell apoptosis in mouse testes by activating caspase-9, BAX, caspase-8, caspase-3, and mitochondrial release of Cyt-C (Wang et al. 2010). In male rats, BPA administration increased apoptosis of testes cells and sperms via BCL2 inhibition (Othman et al. 2016). BPA exposure induced DNA fragmentation in zebrafish ovaries, activated caspase-3, caspase-8, and increased BAX/BCL2 ratio (Biswas et al. 2020). In murine macrophages, BPA-induced apoptosis via caspase-dependent and independent mechanisms. The caspase-dependent apoptosis involved activation of Cyt-C through inhibition of BCL2 and BCL-XL, activation of BAX, BID, and BAD, and induction of caspase-3 and -9, resulting in poly(ADP-ribose) polymerase 1 (PARP1) activation. The caspase-independent apoptosis induction in RAW264.7 macrophages involved nuclear translocation of apoptosis-inducing factor (AIF) (Huang et al. 2018). BPA exposure elevated the expression of Cyt-C, AIF, and caspase-3/9 and reduced the levels of BCL2 in spermatogenic cells (Wang et al. 2014). BPA triggered mitochondrial damage by impairing the levels of pro-apoptotic and anti-apoptotic proteins, resulting in increased release of Cyt-C to the cytosol (Lin et al. 2013). Besides, BPA-induced oxidative stress and inflammatory response by activating MAPK, PI3K-AKT, and NF-κB signaling (Gassman 2017; Nomiri et al. 2019). In colonic epithelial cells, treatment with BPA increased mitochondrial and cytosolic ROS, malondialdehyde, and H_2O_2 levels, depolarized MMP, and triggered apoptosis via MAPK and AKT signaling (Qu et al. 2018). BPA exacerbated GC-2 cell injury by activating caspase-3 and increasing mitochondrial Cyt-C release (Lee et al. 2013). Neuroblastoma cells treated with BPA showed diminished BCL2 expression with simultaneous upregulation of Cyt-C, caspase-3, BAX, and BAK1 proteins (Wang et al. 2021). BPA exposure to ARPE-19 cells decreased mitochondrial BCL-XL expression with a concomitant increase in BAX expression (Chiang et al. 2022). 4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene is a known metabolite of BPA. Exposure of Neuro 2a cells to this metabolite elevated mitochondria-dependent apoptosis and resulted in neuronal cell death (Huang et al. 2021). Collectively, these findings insinuate the capability of BPA to induce apoptosis by altering mitochondrial signaling.

Mitophagy

Mitophagy is the process of removal of damaged or defective mitochondria. It plays a vital role in mitochondria's quality control and turnover to maintain normal cellular functions (Pickles et al. 2018). Additionally, it plays a crucial role in the degradation of paternal mitochondria and pathological conditions such as cancer and neurodegenerative disorders (Um and Yun 2017). In mammals, the PINK1-PARKIN signaling pathway regulates mitophagy (McWilliams and Muqit 2017). Several recent findings have shown that premature activation of mitophagy is crucial in BPA-induced mitochondrial dyshomeostasis. Studies conducted in male Wistar rats have reported the role of BPA in impairing the mitophagy pathway. Further, after BPA exposure, the induction of kidney injury and elevated levels of PINK1 and PARKIN were observed in liver tissue (Peerapanyasut et al. 2019). The hippocampus exposed to BPA showed impaired neurogenesis and mitophagy (Agarwal et al. 2016). BPA exposure resulted in aberrant expression of several nuclear-encoded genes linked with mitophagy. For instance, a systematic toxicological investigation using CRISPR screening suggested the need for UGT1A9 in BPA-induced mitochondrial dysfunction (Tian et al. 2022). In mice having wild-type UGT1A9, BPA-induced liver injury was associated with mitophagy inhibition, while silencing of UGT1A9 diminished the adverse effects of BPA. BPA exposure induced mitophagy in primary rat hepatocytes via PINK1 accumulation and PARKIN translocation to damaged mitochondria (Anand et al. 2020). BPA-related tissue injuries show mitochondrial structural and functional modifications and mitophagy (Peerapanyasut et al. 2019, 2020). Antioxidant therapy using N-Acetylcysteine reduced mitophagy and acute kidney injury caused by BPA exposure. In BHPF-treated oocytes showed mitophagy coupled with increased expression of PINK1, Beclin1 (BECN1), and microtubule-associated proteins 1A/1B light chain 3B (MAP1LC3B), and a decrease in the expression of the translocase of outer mitochondrial membrane 20 (TOMM20) and TOMM17A (Jiao et al. 2019). BPA exposure can cause mitophagy by

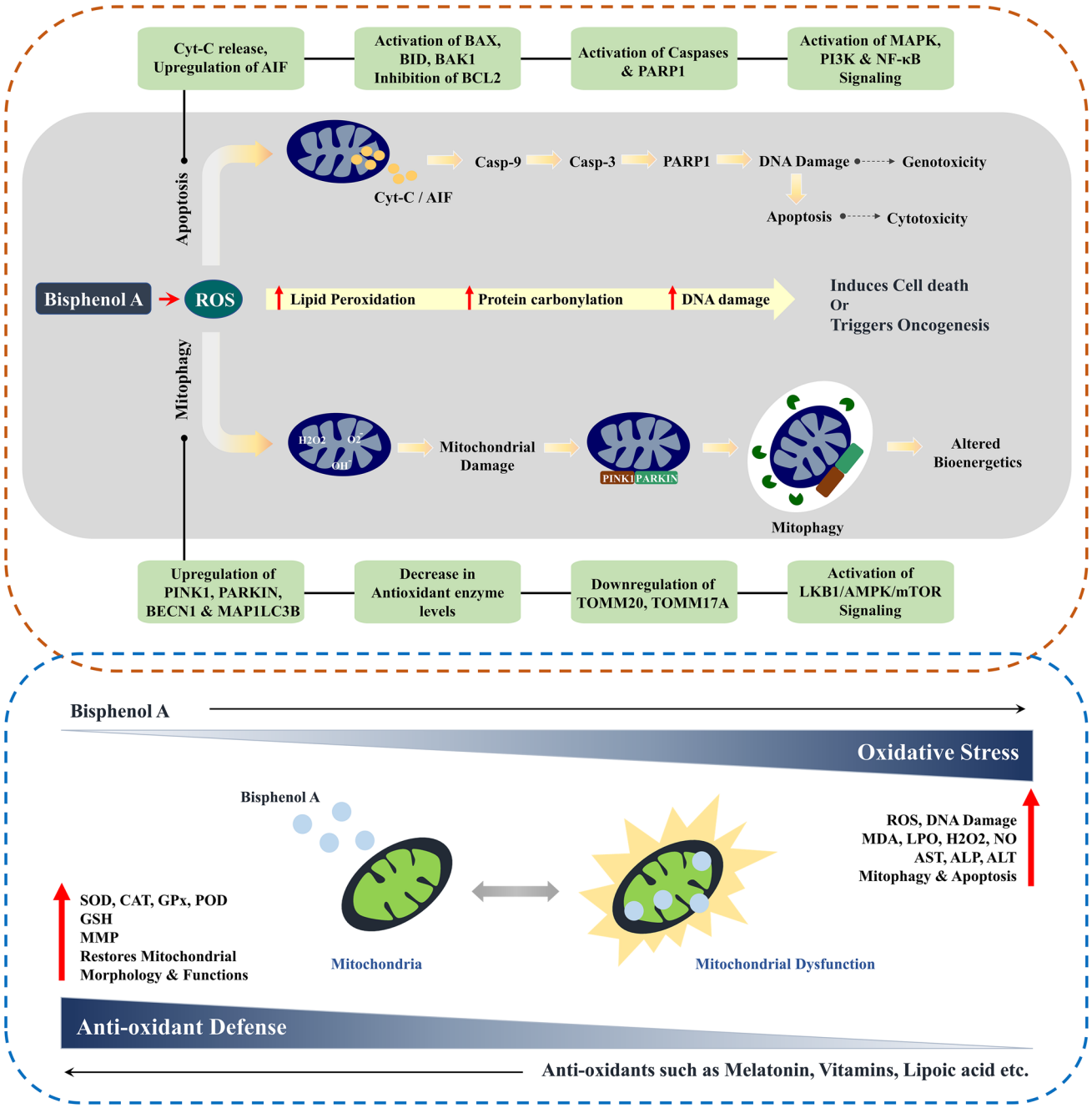

Fig. 3 Effect of BPA-induced oxidative stress on apoptosis and mitophagy. BPA-induced ROS accumulation elevates lipid peroxidation, DNA damage, and protein carbonylation. Besides, it alters mitochondrial bioenergetics by enhancing PINK-PARKIN-mediated mitophagy. BPA exposure activates apoptotic proteins and thereby imparts its genotoxic/cytotoxic effects. BPA promotes cell death or neoplastic progression by modulating mitochondrial structure and function. The toxicological effects of BPA are mainly due to elevated oxidative stress. Treatment with antioxidant agents such as melatonin, lipoic acid, and vitamins can restore mitochondrial functionality and mitigate BPA's toxic effects

activating autophagic flux. For example, LKB1/AMPK/mTOR axis activation has been shown to contribute to autophagy induction in rat primary hepatocytes and may participate in mitophagy induction (Anand et al. 2020).

Mitochondrial mass and mitochondrial biogenesis are interconnected. Several findings have demonstrated that alterations in mitochondrial mass can contribute to various diseases (Kobroob et al. 2018; Meli et al. 2020). Changes in mitochondrial mass could be a possible metabolic biomarker

for cancer (Lamb et al. 2015). In INS1 cells, BPA treatment (0.002–2 µM for 48 h) significantly reduced mitochondrial mass and cellular ATP and resulted in MMP disruption (Lin et al. 2013). BPA-mediated mitochondrial dysfunction may involve the activation of pathways leading to mitophagy induction, thus interfering with mitochondrial mass (Fig. 3). Table 2 summarizes different findings depicting the effects of BPA on the mitochondrial structure.

Bioenergetics and Respiration

By altering cellular bioenergetics, environmental agents contributed to numerous diseases (Kasperski and Kasperska 2018). Reports have shown that BPA affects bioenergetics by disturbing mitochondrial proteins involved in modulating bioenergetics (Marroqui et al. 2018) (Table 3). For instance, exposure of pancreatic islets to BPA (25 µg/L) led to mitochondrial swelling, diminished Cyt-C oxidase activity, and ATP levels (Marroqui et al. 2018). A research group has demonstrated that exposure to an environmental dose of BPA (1 nM) significantly augmented the expression of genes linked to OXPHOS and mitochondrial function, such as ubiquinol-Cyt-C reductase binding protein (*UQCRB*), ATPase Na^+/K^+ transporting subunit β1 (*ATP1B1*), and isoleucyl-tRNA synthetase (*IARS*) (Carchia et al. 2015). Uncoupling protein 2 (*UCP2*) is a member of the mitochondrial anion carrier family and is vital for controlling proton flux uncoupling in mitochondria (Pierelli et al. 2017). BPA exposure activated *UCP2* expression in INS1 cells (Lin et al. 2013). Also, in *UCP2* overexpressing islet cells, an inverse correlation was observed between *UCP2* expression and ATP levels (Lin et al. 2013). The adult rats exposed to BPA (40 µg/kg/day) showed significantly reduced mitochondrial complex activities and ATP production (Lin et al. 2013). Prenatal exposure to BPA (50 µg/kg/day) downregulated Cyt-C expression in heart tissue of neonatal rats (Marroqui et al. 2018). 3T3-L1 adipocytes treated with BPA (10 nM), nonylphenol (600 pM), and diethylstilbestrol (0.23 pM) displayed reduced respiration, ATP production and glycolytic functions (Tsou et al. 2017). BPA-induced impaired mitochondrial bioenergetics may contribute to hepatotoxicity. In Wistar rats, a high dose of BPA (500 mg/kg for 14 days) significantly affected ETC complex activities with a concomitant increase in lipid peroxidation and hepatotoxicity (Khan et al. 2016).

BPA exposure negatively affected intracellular ATP levels in mouse spermatozoa (Rahman et al. 2016). BPA lowered murine pancreatic cell viability by altering mitochondrial function. Besides, co-exposure to low concentrations of BPA (1 nM) and glucose (25 mM) depleted intracellular ATP levels suggesting impaired bioenergetics (Carchia et al. 2015). BPA diminished intracellular ATP by uncoupling OXPHOS, inhibiting respiration and thus altering mitochondrial activity (Gassman 2017). BPA affected sperm function by targeting mitochondrial and cellular ATP via activation of the kinase pathway (Rahman et al. 2016). The same study showed that BPA exposure altered the expression of genes belonging to energy metabolism, stress response, ROS metabolism, cytoskeletal/structural proteins, and fertility-related proteins (Rahman et al. 2016). Dietary intake of BPA affected the activities of mitochondrial complexes IV and V and reduced intracellular ATP levels in mouse colon and liver tissue (Wang et al. 2019b). Exposure to BPA may induce mitochondrial dysfunction to foster PCOS (Rutkowska and Rachoń 2014; Matuszczak et al. 2019). HepG2 cells treated with BPA (10 and 100 nM for 2–12 h) displayed reduced oxygen consumption rate and ATP production resulting in altered mitochondrial morphology and functionalities (Moon et al. 2012).

BPA-exposed rats showed enhanced protein oxidation, lipid peroxidation, and substantial reduction in the enzymes of mitochondrial complex I–V (150, 250, and 500 mg/kg for 14 days) (Khan et al. 2016). In mice, oral administration of BPA (10 mg/kg) for 14 days diminished mitochondrial enzyme activities, including malate dehydrogenase, NADH dehydrogenase, succinate dehydrogenase, monoamine oxidase, and isocitrate dehydrogenase (Anjum et al. 2011). Mitochondrial enzyme activity declined in BPA-treated rats (10 mg/kg of BPA for 14 days), and subsequent testicular dysfunction was observed (El-Beshbishy et al. 2013). A recent study using *Caenorhabditis elegans* showed that exposure to 1 mM BPA shortened life span and increased the age-related changes in neurons with a concomitant decline in oxygen consumption rate and MMP (Hyun et al. 2021). Taken together, various experimental evidence in numerous cells or tissue types emphasize the potency of BPA to impair bioenergetics, ATP levels, and mitochondrial respiration (Table 3).

Approaches to Mitigate the Toxicological Effects of BPA

BPA-induced mitochondrial dysfunction plays a crucial role in the pathogenesis of many diseases (Meli et al. 2020). Activation of the oxidative stress pathway is an effective mechanism of BPA-mediated mitochondrial dysfunction (Gassman 2017). Thus, targeting the oxidative stress pathway can help reverse the toxicological effects of BPA. In this direction, several previous investigations have demonstrated the ability of vitamins and co-factors, natural extracts, melatonin, selenium, and methyl donors to reverse the toxicological effects exerted by BPA (Anjum et al. 2011; Khalaf et al. 2019; Meli et al. 2020) (Table 4). This section describes various approaches to reverse the mitochondrial dysfunction caused by BPA. For instance, astaxanthin (ATX) treatment restored BPA-induced reduction in mitochondrial complex

Table 2 Effects of BPA on mitochondrial structure

Experimental model and dosage of BPA used	Effect	References
BPA and MMP		
HepG2 cells (1 pM, and 0.67 mM BPA for 24, 48 and 72 h)	Hyperpolarization of MMP and disrupts mitochondrial function	Huc et al. (2012)
Pancreatic islets of C57/B6 male mice (1 nM BPA for 48 h)	Impairs MMP and induces mitochondrial dysfunction	Carchia et al. (2015)
HepG2 cells (10 and 100 nM BPA for 2 h)	Decreases MMP and disrupts mitochondrial dynamics	Moon et al. (2012)
Mouse Sertoli TM4 cells (0.34 µM, 0.34 mM BPA for 24 h)	Reduces mitochondrial density, MMP and affects mitochondria-mediated pathways	Ge et al. (2014)
Pregnant Wistar rats (examined in neonatal rats; 50 µg/kg/day BPA throughout gestation)	Decreases matrix density and MMP	Jiang et al. (2014a)
Male Wistar rats (50 µg/kg/day BPA since delectation to 24 and 48 weeks)	Hypermethylation of *PGC1α*, dissipates MMP and impairs mitochondrial function	Jiang et al. (2015)
Human renal proximal tubular epithelial cells (200 µM BPA for 24 h)	Increases MMP and intracellular Ca^{2+}	Bosch-Panadero et al. (2018)
Lymphoblastoid cell lines (25, 50, and 100 mM BPA for overnight)	Decreases MMP	Kaur et al. (2014)
Human colonic goblet cell line (LS174 T) (150 µM/mL BPA for 24 h)	Decreases MMP and alters normal mitochondrial function	Zhao et al. (2019)
HCT116 cells (250 µM BPA for 24 h)	Reduces MMP and mitochondrial integrity and enhances intracellular Ca^{2+}	Qu et al. (2018)
BPA and mtDNA copy number and DNA damage		
FRTL-5 thyroid cells (1 nM BPA for 1, 3, and 7 days)	Induces DNA damage	Porreca et al. (2016)
HepG2 cells (0.1 and 10 µmol/L BPA for 24 h)	Induces genotoxicity and DNA strand breaks	Fic et al. (2013)
Lymphoblastoid cell lines (25, 50, and 100 mM BPA for overnight)	Enhances mtDNA copy number	Kaur et al. (2014)
INS-1 pancreas cell line (25, 50, and 100 µM BPA for 24 h)	Induces DNA damage in INS-1cells	Xin et al. (2014)
Male CD-1 mice (50 µg/kg/day BPA for 10 weeks)	Reduces mtDNA copy number	Wang et al. (2019b)
Parthenotes (Embryonic stem cell; 100 µM BPA for 3 days)	Causes DNA damage through p53-p21 signaling pathway	Guo et al. (2017)
Adult rats (10 µg, 5 mg, and 50 mg/kg bw BPA for once a day for 6 days)	Increases DNA strand breaks and exhibit genetic toxicity	Tiwari et al. (2012)
Adult male Sprague–Dawley rats (200 mg/kg bw/day BPA for 10 days)	Increases DNA damage in rat spermatocytes and increases the number of H2AX-positive foci	Wu et al. (2013)
BPA and mitochondrial structural alteration and mitophagy		
Rat insulinoma (INS-1) (0.0020, 0.02, 0.2, or 2 µM BPA for 48 h)	Induces mitochondrial fragmentation and alters mitochondrial network organization	Lin et al. (2013)
Wistar rats (50, 250, or 1250 µg/kg/day BPA throughout gestation and lactation)	Induces mitochondrial swelling and rough endoplasmic reticulum dilation, increases mitochondrial density, disrupts lipid homeostasis, and affects glucose homeostasis	Wei et al. (2011)
Pregnant Wistar rats (Examined in neonatal rats; 50 µg/kg/day BPA throughout gestation)	Induces mitochondrial ultrastructural abnormalities, mitochondrial swelling, blurred or broken Cristae	Jiang et al. (2014a)
C57BL/6 male mice (1.2 mg/kg bw/day BPA for 5 days)	Induces hepatic mitochondria swelling and impairs mitochondrial structure and function	Moon et al. (2012)
Male Sprague Dawley rats (2.5, 25, and 250 mg/L BPA for 24 h)	Loss of mitochondrial structural integrity and induces mitochondrial swelling	Song et al. (2012)
BPA and mitochondrial fission		
Hippocampal neural stem cells (100 µM BPA for 24 h)	Upregulates DRP1, enhances mitochondrial translocation and mitochondrial fission and impairs mitochondrial dynamics	Agarwal et al. (2016)
Male Wistar rats (5 and 50 mg/kg BPA for 5 weeks)	Increases protein levels of p-DRP1/DRP1, PINK1 and PARKIN, induces abnormalities in mitochondrial functions, dynamics and mitophagy	Peerapanyasut et al. (2019)

Table 3 Impact of BPA on mitochondrial functions

Experimental model and dosage used	Target	Effect
BPA and mitochondrial respiratory complex (MRC) activity		
Human breast cancer T47D-KBluc cells and 3T3-L1 adipocytes (10 nM BPA for 24 h)	MRC	Disrupts MRC function (Tsou et al. 2017)
Human renal proximal tubular epithelial cells (200 µM BPA for 24 h)	Cyt-C, *NRF2*, HO-1 and NQO-1	Activates NRF2, induces electron leakage from the MRC during oxidative phosphorylation (Bosch-Panadero et al. 2018)
Mouse Neuro2a (neuronal) and GC1 cells (spermatogonia) (50 and 100 µM BPA for 24 and 48 h)	DJ-1	Increases expression of DJ-1, decreases mitochondrial complex-I activity and promotes mitochondrial damage (Ooe et al. 2005)
Human colonic goblet cell line (LS174 T) (150 µM/mL of BPA for 24 h)	MRC complexes I, III, IV and V	Decrease the activity of MRC complexes I, III, IV and V (Zhao et al. 2019)
Pregnant Wistar rats (40 µg/kg/day BPA for gestational day 0 to postnatal day 21)	MRC-I and III, *UQCRC2*, *UQCRFS1*, *ETFA*, and *ATP51*	Decreases MRC-I and III activity, MRC encoded genes and fatty acid metabolism, and downregulates *UQCRC2*, *UQCRFS1* and *ETFA* genes (Jiang et al. 2014b)
Pregnant Wistar rats (50 µg/kg/day BPA throughout gestation)	MRC-II, *ERRA*, *ERRγ*, *PPARA* and *PGC1α*	Decreases MRC-II activity, downregulates the expression of *ERRA*, *ERRγ*, *PPARA* and *PGC-1α* and dysregulates OXPHOS pathway (Jiang et al. 2014a)
Male Wistar rats (50 µg/kg/day BPA since delectation to 24 and 48 weeks)	*PGC1α* and MRC	Hypermethylation of PGC-1α, dissipates and MRC activity (Jiang et al. 2015)
Male CD-1 mice (50 µg/kg/day BPA for 10 weeks)	MRC-IV and V	Decreases the activity of MRC-IV and V (Wang et al. 2019b)
C57BL/6 male mice (1.2 mg/kg bw/day BPA for 5 days)	MRC complex III and IV	Reduces oxygen consumption rate, decreases the expression of MRC-III and V, and impairs mitochondrial structure and function (Moon et al. 2012)
Wistar rats (150, 250, and 500 mg/kg bw BPA for 14 days)	ETC enzyme activity (complexes I–V)	Decreases the enzyme activity of complex I–IV (Khan et al. 2016)
BPA and mitochondrial bioenergetics		
Human breast cancer T47D-KBluc cells and 3T3-L1 adipocytes (10 nM BPA for 24 h)	ATP production	Decreases mitochondria associated ATP production (Tsou et al. 2017)
Human renal proximal tubular epithelial cells (200 µM BPA for 24 h)	ATP level	Declines ATP synthesis and increase oxygen consumption rate (Bosch-Panadero et al. 2018)
Mouse Sertoli TM4 cells (0.34 µM and 0.34 mM BPA for 24 h)	IMMT3, ETFα/β, *UQCRC1*, GLUT3 and Lactate dehydrogenase A	Decreases the expression IMMT3, ETFα/β and UQCRC1 and lactate dehydrogenase A, enhances ATP concentrations, upregulates *GLUT3,* inhibits anaerobic respiration, promotes uptake and consumption of glucose and cell proliferation (Ge et al. 2014)
Rat insulinoma (INS-1) (0.002, 0.02, 0.2, or 2 µM BPA for 48 h)	Cellular ATP level, TFAM, ATP6, OGDH	Reduces cellular ATP levels, downregulates the expression of TFAM, ATP6, OGDH, upregulates UCP2, and mitochondrial depolarization (Lin et al. 2013)
Spermatozoa (0.0001, 0.01, 1, and 100 µM BPA for 6 h)	Effect on ATP level	Negatively affects sperm motility, viability, mitochondrial functions, and intracellular ATP levels (Rahman et al. 2016)
Human colonic goblet cell line (LS174 T) (150 µM/mL BPA for 24 h)	ATP level	Reduces intracellular ATP levels (Zhao et al. 2019)

Table 3 (continued)

Experimental model and dosage used	Target	Effect
Male Wistar rats (50 µg/kg/day BPA since delectation to 24 and 48 weeks)	ATP production	Reduces ATP production and impairs mitochondrial function (Jiang et al. 2015)
Male CD-1 mice (50 µg/kg/day BPA for 10 weeks)	Intracellular ATP content	Reduced the intracellular ATP content (Wang et al. 2019b)
Hepatic mitochondria from Male F344/DuCrj rats (0.25 and 1 mM BPA for 30 min)	Adenine nucleotides, ATP level	Depletes intracellular ATP and total adenine nucleotides, inhibited state-3 oxygen consumption rate (Nakagawa and Tayama 2000)
Male Sprague Dawley rats (2.5, 25, and 250 mg/L BPA for 24 h)	*UCP2*, *OGDH*, *COX*	Increases expression of *UCP2*, downregulates *OGDH* gene expression, decreases COX activity and ATP production and disrupts mitochondrial biogenesis (Song et al. 2012)
BPA and apoptosis		
Pancreatic islets of C57/B6 male mice (1 nM BPA for 48 h)	*BAX*, *BCL2*	Increases *BAX* transcript level and decreases *BCL-2* expression, and promotes apoptosis (Carchia et al. 2015)
Human renal proximal tubular epithelial cells (200 µM BPA for 24 h)	Mitochondria	Promotes mitochondrial injury and apoptosis (Bosch-Panadero et al. 2018)
Mouse Sertoli TM4 cells (0.34 µM and 0.34 mM BPA for 24 h)	*CCND1*, *PCNA*, *BCL2*, procaspase-3	Increases the expression of *PCNA* and *BCL-2* (Ge et al. 2014)
BeWo (Human trophoblast cell lines) (0.09, 0.9 and 9 µM BPA for 48 and 72 h)	HIF1α, BCL2, HSP70, caspase-3	Reduces HIF-1α expression, increases BCL-2 and HSP70 levels, reduces caspase-3 activation, reduces NRF2 levels and delocalisation of nuclear NRF2, increases cell viability and alters cell morphology (Ponniah et al. 2015)
Rat insulinoma (INS-1) (0.002, 0.02, 0.2, or 2 µM BPA for 48 h)	*BAX*, *BCL2*	Reduces Cyt-C, increases *BAX* and reduces *BCL-2* expression, triggers apoptosis and the release of apoptogenic factors (Lin et al. 2013)
Murine macrophage RAW264.7 cells (10, 30 and 50 µM BPA for 24 h)	BCL2, BCL-XL, BAX, BID, BAD, caspase-9, caspase-3, and PARP-1	Phosphorylates Cyt-C and p53, downregulates BCL2 and BCL-X_L and upregulates BAX, BID, and BAD, cleaves caspase-9, caspase-3, and PARP-1, and promotes nuclear translocation of AIF (Huang et al. 2018)
Pancreatic islets of adult male mice (10 µg/kg/day BPA for 2 weeks prior to mating)	UCP2, caspase-3	Increases UCP2 mRNA levels and caspase-3 activity, and impairs mitochondrial function and apoptosis (Bansal et al. 2017)
Spermatozoa (0.0001, 0.01, 1, and 100 µM BPA for 6 h)	MAPK, PI3K and PKA	Activates MAPK, PI3K, and PKA pathways (Rahman et al. 2016)
Parthenotes (Embryonic stem cell; 100 µM BPA for 3 days)	Cyt-C, p53-p21 pathway	Damages mitochondria, release of Cyt-C and induces apoptosis, and activate p53-p21 signaling (Guo et al. 2017)
Human colonic goblet cell line (LS174 T) (150 µM/mL of BPA for 24 h)	Caspase-3, -8, -9 and -10	Upregulates mRNA levels of caspase-3, 8, 9 and 10, and elevates apoptosis (Zhao et al. 2019)
HCT116 cells (250 µM BPA for 24 h)	Caspase-3, -8, -9 and *BAX*	Upregulates caspase 3, 8, and 9 activities, enhances *BAX* expression and promotes apoptosis (Qu et al. 2018)

ERR estrogen-related receptor; *ETF* electron transfer flavoprotein; *HCT* human colorectal carcinoma; *IMMT* inner membrane mitochondrial protein; *OGDH* oxoglutarate dehydrogenase; *OXPHOS* oxidative phosphorylation; *GLUT3* glucose transporter 3; *HO-1* heme oxygenase 1; *NQO-1* NAD(P)H dehydrogenase[quinone]1; *DJ-1* activated Ras-dependent oncogene; *ETFα/β* electron transfer flavoprotein; *PKA* protein kinase A

Table 4 Compounds which alleviate BPA-induced toxicity

Compound and dosage used	Experimental model	Effect
Selenium (0.5 ppm sodium selenite/kg diet for 8 weeks)	Male BALB/c mouse	Reduces ROS and lipid peroxidation and histopathological changes in testes of mice (Kaur et al. 2018)
1,25-Dihydroxyvitamin D3 (1,25D3) (0.1 µM for 30 min)	Granulosa cells from female Sprague–Dawley rat	Prevents mitochondrial DNA deletion in female ovary, promotes TFAM, COX1 protein expression, increases mitochondrial respiration and ATP production (Lee et al. 2019)
Green tea (10–50 µg/mL for 4 h)	Human erythrocytes	Reduces hemolysis and OS (Suthar et al. 2014)
Gallic acid (20, 40, 80 µg/mL for 1 h)	Male Charles Foster rat	Counteracts BPA-induced alterations in mitochondrial intactness, lipid peroxidation and protein carbonylation (Dutta and Paul 2019)
Tannins from *Rhus typhina* (1–50 µM for 30 min)	Human erythrocytes	Inhibits hemolysis and methemoglobin formation, increases intracellular GSH in erythrocytes, and enhances rigidity of erythrocyte membrane (Olchowik-Grabarek et al. 2018)
Taurine (30 and 50 µmol/L for 2 h)	Testicular mitochondria from NMRI mouse sperm	Suppresses mitochondrial OS, enhances MMP, and improves sperm motility and viability (Rezaee-Tazangi et al. 2020)
Coenzyme-Q10 (100 µg/mL for 24 h)	*Caenorhabditis elegans*	Rescues against reproductive toxicity induced by BPA (Hornos Carneiro et al. 2020)
Vitamin B12 (150 µg/kg), Vitamin B9 (15 mg/kg), Choline (400 mg/kg), and Betaine (3 g/kg) from day 0 to 90 of gestation	Female pig	Increases SOD, CAT, and GPx activity and decreases homocysteine levels, OS in sows (Mou et al. 2018)
Glutathione + Vitamin E (5 + 2 mM for 6 h)	Sperm from CD-1 (ICR) male mouse	Reduces ROS and increases intracellular ATP levels, prevents motility loss and abnormal acrosome reaction in BPA-exposed spermatozoa (Rahman et al. 2019)
Vitamin E (4 mg/100 g bw for 90 days)	Wistar albino rat	Improves male fertility, protects testicular cells and epididymal sperm from BPA-induced apoptosis (Srivastava and Gupta 2018)
All-trans-retinoic acid (5 mg/kg for 3 days)	Female Crj:CD (SD) ovariectomized rat	Reduces BPA-induced uterine weight (Koda et al. 2007)
Melatonin (10 mg/kg/day for 5 weeks)	Wistar Rat	Decreases OS, maintains redox equilibrium within the mitochondria (Kobroob et al. 2018)
Lycopene (10 mg/kg for 30 days)	Female Wistar rat	UpregulatesCYPR450 which in turn clears BPA metabolites rapidly, improves liver function biomarkers, oxidant-antioxidant state and DNA damage (Abdel-Rahman et al. 2018)
Lipoic acid (20 mg/kg for 14 days)	Male albino rat	Restores mitochondrial marker enzyme activities and increases antioxidant levels in mitochondria (El-Beshbishy et al. 2013)
Folic acid (20 mg/kg/day for 14 days)	Male Wistar rat	Increases serum testosterone, and decreases number of TUNEL positive cells (Gules et al. 2019)
Crocin (20 mg/kg/day for 30 days)	Male Wistar rat	Improves antioxidant defend system, cellular glutathione and reduces 8-isoprostane in liver (Vahdati Hassani et al. 2017)
Sesame lignans (20 mg/kg bw for 6 weeks)	Male Wistar albino rat	Reduces serum AST, ALT, total bilirubin, Serum TG, TC, LDL-C, VLDL-C and LDH, enhances SOD, GSH and HDL-C levels (Eweda et al. 2019)
Astaxanthin (25 mg/kg/day for 5 weeks)	Male Wistar rat	Reduces BPA-induced nephrotoxicity by protecting mitochondrial function to regulate redox balance, inflammatory response, and apoptosis (Jiang et al. 2020)
Adiantum capillus-veneris L. extract (25 mg/kg for 15 days)	Male albino rat	Increases total antioxidative capacity of the testes, restores serum testosterone level and spermatogenesis (Yousaf et al. 2016)

Table 4 (continued)

Compound and dosage used	Experimental model	Effect
Naringin (40, 80, 160 mg/kg for 30 days)	Wistar rat	Reduces BPA-induced cardiotoxicity by lipid-lowering properties, antioxidant activity, and suppressing lipid peroxidation (Khodayar et al. 2020)
Cuscuta chinensis flavonoids (40 mg/kg from gestation day 0.5 to 17.5)	Kunming mouse	Blocks the transcription and translation of caspase-7 and -9 in the testes of male offspring (F1 mice) (Wei et al. 2019)
Nano-micelle curcumin (50 mg/kg for 4 weeks)	Male Wistar rat	Reduces MDA levels and blood pressure in heart tissue and elevates GSH levels (Valokola et al. 2019)
Vitamin C + Vitamin E (50 + 50 mg/kg for 30 days)	Female Wistar albino rat	Reduces apoptotic cell death in rat ovaries (Bilgi et al. 2019)
Quercetin (75 mg/kg for 14 days)	Wistar Rat	Decreases ROS, MMP and MDA levels (Mahdavinia et al. 2019)
N-acetylcysteine (NAC) (100 mg/kg for 5 weeks)	Male Wistar rat	Diminishes liver functional impairment, OS, inflammation, and apoptosis, alleviates abnormalities in mitochondrial functions, dynamics, mitophagy, and ultrastructure of the liver by improving AMPK-PGC1α-SIRT3 signaling (Peerapanyasut et al. 2019)
Withania somnifera root extract (100 mg/kg bw/day for 1 week)	Male Swiss albino mouse	Restores the number of NMDA receptors in hippocampus region and ameliorates endogenous antioxidant level in brain (Birla et al. 2019)
Quercus dilatata Lindl. ex Royle extract (150 and 300 mg/kg bw for 4 weeks)	Sprague Dawley rat	Reduces ALT, H_2O_2, nitrite, erythrocyte sedimentation rate, DNA damage and histopathological injuries, enhances SOD, CAT, GPx and GSH levels (Kazmi et al. 2018)
Ipomoea batatas L. Lam. Extract (150 mg/kg and 300 mg/kg for 21 days)	Sprague Dawley rat	Enhances sexual excitement, improves semen quality, testosterone, FSH, LH, and estradiol levels, restores CAT, SOD, POD, GSH and reduces NO abundance (Majid et al. 2019)
Murraya koenigii extract (200 mg/kg for 8 weeks)	Male Balb/c mice	Improves sperm parameters and reduces LPO, ROS and apoptotic proteins in the testes of treated mice (Kaur et al. 2020)
Tualang honey (200 mg/kg for 6 weeks)	Female Sprague rat (P21)	Improves uterine morphological abnormalities, reduces LPO, and normalizes ERα, ERβ, and C3 expressions and distribution (Mohamad Zaid et al. 2015)
Cordyceps militaris extract (200–800 mg/kg for 4 weeks)	Sprague–Dawley rat	Reduces OS and testicular histopathological changes, and improves antioxidant enzyme activity and GSH levels (Wang et al. 2016)
Ginger (250 mg/kg bw for 35 days)	Male albino rat	Protects DNA of the thyroid gland from fragmentation, improves thyroid iodide uptake by upregulation of *NIS*, *TPO* and *TSHR* gene expressions with a subsequent increase of thyroid hormone synthesis (Mohammed et al. 2020)
Aloe vera extract (300 mg/kg for 8 weeks)	Male Wistar rat	Accelerates total antioxidant capacity and restores testicular tissue structure (Behmanesh et al. 2018)
Asparagus officinalis extract (400 mg/kg/day for 8 weeks)	Male Wistar rat	Decreases AST, ALP, ALT, bilirubin, urea and serum creatinine and MDA and improves GSH levels (Poormoosavi et al. 2018)
Pumpkin seed oil (1 mL/kg/day for 28 days)	Male Swiss albino mouse	Reduced DNA damage and improves histopathological alterations in liver and testes tissues (Fawzy et al. 2018)

OS oxidative stress; *BPA* bisphenol A; *ROS* reactive oxygen species; *MMP* mitochondrial membrane potential; *SOD* superoxide dismutase; *CAT* catalase; *LDH* lactate dehydrogenase; *NO* nitric oxide; GSH glutathione; *MDA* malondialdehyde; *GPx* glutathione peroxidase; *AST* aspartate aminotransferase; *ALT* alanine transaminase; *ALP* alkaline phosphatase; *TG* triglyceride; *TC* total cholesterol; *LDL-C* low density lipoprotein cholesterol; *VLDL-C* very low density lipoprotein cholesterol; *HDL-C* high-density lipoprotein cholesterol; *POD* peroxidase; *LPO* lipid peroxidation

activity in kidney tissues (Jiang et al. 2020). Treatment with 1,25-dihydroxy vitamin D3 (1,25-D3) may help reduce the toxicity of BPA in reproductive cells. Besides, 1,25-D3 increased mtDNA content, biogenesis, ATP production, and cellular oxygen consumption rate via PI3K-AKT signaling to minimize reproductive toxicity in ovarian granulosa cells (Lee et al. 2019). BPA exposure induces apoptosis in various cell types via mitochondria-dependent and independent pathways (Wang et al. 2019b). A study showed that treatment with melatonin could control apoptosis, protect testes, and improve sperm quality against BPA (Othman et al. 2016). BPA disrupted thyroid hormone synthesis and metabolism in rats and induced pathological changes by increasing inducible nitric oxide synthase and decreasing *NRF2* expression. Treatment with ginger extract protects against BPA-induced thyroid damage by targeting the oxidative pathway and restoring antioxidant balance (Mohammed et al. 2020). Another study showed that α-lipoic acid treatment reversed the neuro-behavioral toxicity induced by BPA (Khan et al. 2018). In rat liver, quercetin protects against BPA-induced mitochondrial toxicity (Mahdavinia et al. 2019). *N*-Acetyl Cysteine (NAC) is a powerful antioxidant extensively used to relieve oxidative stress (Kobroob et al. 2021). Male Wistar rats exposed to BPA showed mitochondrial swelling and increased ROS production in the renal tissue (Kobroob et al. 2021). NAC treatment restored mitochondrial integrity and oxidative balance by modulating the AMPK-SIRT3-SOD2 axis (Kobroob et al. 2021). Thus, NAC can be used to prevent the renal toxicities caused due to long-term exposure to BPA. Additionally, in ARPE-19 cells, BPA-induced oxidative stress and cytotoxicity were significantly reduced upon treatment with NAC (Chiang et al. 2022). Coenzyme-Q10 (CoQ10), a powerful antioxidant, has reduced apoptosis induced by BPA. The reduced incidence of apoptosis upon CoQ10 treatment involved decreased ROS levels and improved MMP (Liu et al. 2021). Selenium treatment reversed testicular oxidative stress induced by BPA exposure in mouse model (Rafiee et al. 2021). These data suggest the indispensable role of antioxidant treatment in protecting cells against BPA-induced toxicity.

Conclusion and Future Directions

Despite long-standing safety concerns, various consumer products still use BPA for their production. A plethora of experimental evidence has clearly illustrated the adverse health effects of BPA. The current review summarized the data available in published literature related to the impact of BPA on mitochondrial structure, function, and signaling. Our literature review shows that BPA-induced cellular and molecular alterations are corroborated with impaired mitochondrial structure and function. Further, the mitochondrial toxicities in in-vitro and in-vivo models depend on the dose and duration of BPA exposure. Furthermore, BPA can bring about changes to mitochondria at extremely low doses. The findings of several elegant studies have revealed the role of BPA in modulating mitochondrial biogenesis, bioenergetics, and mitochondria-mediated signaling. However, many studies have used doses higher than the concentration of BPA found in the environment. Towards this, we have highlighted some of the research gaps that require detailed investigation, such as:

- More comprehensive, systematic, and mechanistic studies like the CLARITY-BPA study need to be undertaken using environmentally relevant doses of BPA to understand its toxicological aspects in general and mitochondrial dysfunction in particular.
- Large-scale epidemiological analyses using organoid models are lacking to verify the toxicological effects of BPA on mitochondrial functions in humans.
- Restoring the mitochondrial function via treatment with antioxidant agents or through mitochondria transfer or mitochondria replacement therapy could be attempted to reverse the toxic effects of BPA (Fig. 3).
- Most studies have focused on the oxidative stress pathway upon BPA exposure. Future investigations should also examine the involvement of alternative pathways responsible for BPA-mediated mitochondrial impairments.
- Tissue-specific exposure assessments at genomic, epigenomics, transcriptomic, and proteomic levels should be undertaken to comprehensively understand the impact of BPA exposure at the cellular level.

Acknowledgements We thank ICMR-Senior Research fellowship (Reference ID-2019/4115/CMB/BMS), Government of India, the Directorate of Minorities Fellowship (DOM/FELLOWSHIP/CR-10/2019-20), Government of Karnataka, and Dr. TMA Pai Structured Ph.D. fellowship, Manipal Academy of Higher Education (MAHE) for financial assistance. We acknowledge the Centre for DNA repair and Genome Stability (CDRGS), MAHE, Manipal, Karnataka.

Funding Open access funding provided by Manipal Academy of Higher Education, Manipal. No funding was received to assist with the preparation of this manuscript.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical Approval Not applicable.

Consent for Publication The authors have approved the final draft of the manuscript.

Consent for Participation Not applicable.

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