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Addressing Oxidative Stress and Bisphenol A (BPA) Toxicity with Antioxidant Interventions for Male and Female Reproductive Health

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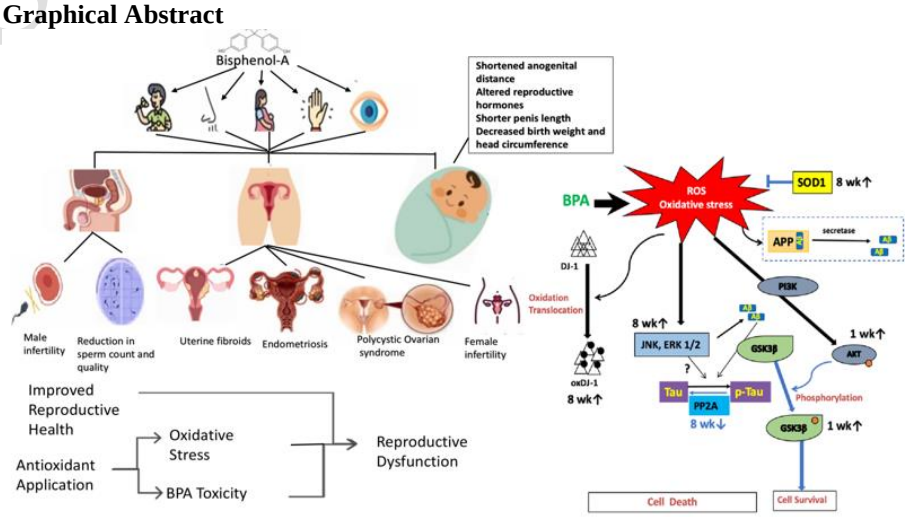
ABSTRACT

Human exposure to bisphenol A (BPA) is protracted since it is a non-persistent anthropogenic molecule that is widely used, found in numerous consumer products, and ubiquitous in the environment. This review looks at the landscape. Numerous research that have looked at the underlying molecular mechanisms of BPA toxicity over the past ten years have linked BPA-induced oxidative stress to human disease, male and female reproductive abnormalities, and other receptors in target cells due to its hormone-like property, which causes undesirable cellular reactions linked to inflammation and oxidative stress. BPA is a metabolic and endocrine disruptor that damages redox equilibrium by decreasing antioxidant enzymes and increasing oxidative mediators. This results in mitochondrial malfunction, changes to cell signaling pathways, and the activation of apoptosis. In order to comprehend how the activation of oxidative stress can be seen as the "fil rouge" of BPA's harmful modes of action with pleiotropic effects, this review will look at the current state of the BPA literature. Here, we focus on the protective effects of five classes of antioxidants vitamins and co-factors, natural products (herbals and phytochemicals), melatonin, selenium, and methyl donors (used alone or in combination) that have been found useful to counteract BPA toxicity in male and female reproductive functions.

Graphical Abstract



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INTRODUCTION

Endocrine-disrupting chemicals (EDCs) are a broad category of compounds that can affect metabolic and reproductive processes as well as interfere with hormonal-signaling pathways (Sifakis, Androutsopoulos, Tsatsakis, & Spandidos, 2017). The most common EDC in the environment today is bisphenol A (BPA), a non-persistent anthropic chemical that has been used extensively in recent decades as a component of plastic for a variety of purposes such as food packaging, personal care, household products, and medical equipment (Meli, Monnolo, Annunziata, Pirozzi, & Ferrante, 2020). In fact, BPA has been found in food, household dust, consumer goods, aquatic ecosystems, the atmosphere, and biotic matrices. Exposure to BPA is associated with deleterious health effects for animals and humans and affects not only endocrine and reproductive organs but also immune and central nervous systems through several mechanisms, including oxidative stress (Abraham & Chakraborty, 2020). Growing evidence from research on laboratory animals shows that this non-persistent compound alters male and female reproductive function even at extremely low exposure levels. This is relevant because BPA exposure may be chronic, making it functionally equivalent to a persistent compound (Nelson, Bhutta, Harris, Danese, & Samara, 2020).

The mechanisms underlying BPA toxicity may be related to its chemical properties in the body, including interactions with hormone receptors (i.e., estrogen receptors) in target cells (Cimmino et al., 2020). As a weak estrogen receptor ligand, BPA binds to the classical nuclear receptors with different affinity, for example, estrogen receptor (ER) α less than ER β (about10,000 times lower than17-β-estradiol), an ditspotency of action becomes higher when the estradiol level is at very low concentrations (Toporova & Balaguer, 2020). BPA also binds many other membranes and nuclear receptors, activating them at concentrations lower than those required to activate ERs (Cimmino et al., 2020). In particular, BPA binds to the membrane-bound form of estrogen receptor (mER) α and G protein-coupled receptor (GPR) 30, inducing non-genomic effects (Maniradhan & Calivarathan, 2023). GPR30 has been detected in several cell types, and it is involved in cell proliferation and apoptosis (Hernández-Silva, Villegas-Pineda, & Pereira-Suárez, 2020). Indeed, seminoma proliferation is induced by allow concentration of BPA through a GPR 30 non-genomic activation. BPA also binds to another estrogen-related receptor (ERR) γ, an orphan nuclear receptor highly expressed in the fetal brain and placenta by which BPA influences fetal tissue development (Cimmino et al., 2020).

As demonstrated by the scientific literature on BPA occurrence in human tissues and body fluids (i.e., urine, serum, plasma, saliva, breast milk, semen, follicular fluids, and adipose tissues), widespread contamination and dietary consumption have resulted in BPA exposure in the general population (Hahladakis, Iacovidou, & Gerassimidou, 2023). According to a recent epidemiological investigation, female reproduction may be adversely affected by elevated urine BPA concentrations in humans (Stavridis, Triantafyllidou, Pisimisi, & Vlahos, 2022). Moreover, BPA exposure has been linked to lower libido and erectile dysfunction in men, and urine BPA levels have been linked to aberrant semen parameters. When exposure happens in utero, the overall effects of BPA on male reproduction seem to be more detrimental (Pivonello et al., 2020). Animal models are crucial for evaluating the underlying toxic mechanisms seen in people, given the difficulties in both tissue sample collection and human exposure evaluation (Wetherill et al., 2007). In the first place, rats vary from humans in that they permit tissue and cell-specific molecular analysis in addition to histological evaluation of diverse tissues (Gignac & Zajenkowski, 2023).

Furthermore, rodent models offer outstanding chances for sex-specific assessments. The tissue under examination, the structural, functional, and epigenetic variations across gender and species, the duration of exposure, and the chemical dosage are all crucial elements to take into account in the experimental design (McKay et al., 2023). Third, a multitude of animal studies have demonstrated that BPA impacts multiple reproductive outcomes, even in spite of the limitations inherent in clinical trials (Cloughesy et al., 2019). Firstly, in contrast to humans, rodents permit tissue- and cell-specific genetic analysis in addition to histological evaluation of a variety of tissues. Secondly, rodent models offer exceptional chances for sex-specific assessments (Edmonds, Caldwell, Brondizio, & Siani, 2020). Important aspects that need to be taken into account in the experimental design include the tissue under examination, the structural, functional, and epigenetic changes between gender and species, the duration of exposure, and the dosage of the chemical (Jeremias, Gonçalves, Pereira, & Asselman, 2020). Third, numerous animal studies have demonstrated that BPA has an impact on multiple reproductive outcomes, even in spite of the limitations of clinical trials. Important aspects that need to be taken into account in the experimental design include the tissue under examination, the structural, functional, and epigenetic changes between gender and species, the duration of exposure, and the dosage of the chemical (Jeremias et al., 2020).

Third, numerous animal studies have demonstrated that BPA has an impact on multiple reproductive outcomes, even in spite of the limitations of clinical trials (Peretz et al., 2014). Oxidative stress and similar indicators are linked to BPA toxicity in a number of animal models, as well as in people (Meli et al., 2020). Growing research indicates that BPA organ damage is largely caused by the generation of Reactive Oxygen Species (ROS) and a reduced ability to defend against antioxidants, which changes the oxidative equilibrium in the mitochondria and throughout the cell (M. S. Amjad et al., 2020). In order to determine that oxidative stress is the leitmotif underpinning BPA's mechanism of action with pleiotropic effects on reproduction, this review provides fresh insights and an up-to-date literature scan on these topics (Burton & Jauniaux, 2011). Additionally, the study explores the impact of antioxidant compounds on BPA-induced toxicity and evaluates their potential effectiveness as a therapeutic approach to mitigate harm to the male and female reproductive organs and their functions (Sánchez-Cruzado, Santiago Campión, & Sánchez-Compaña, 2021).

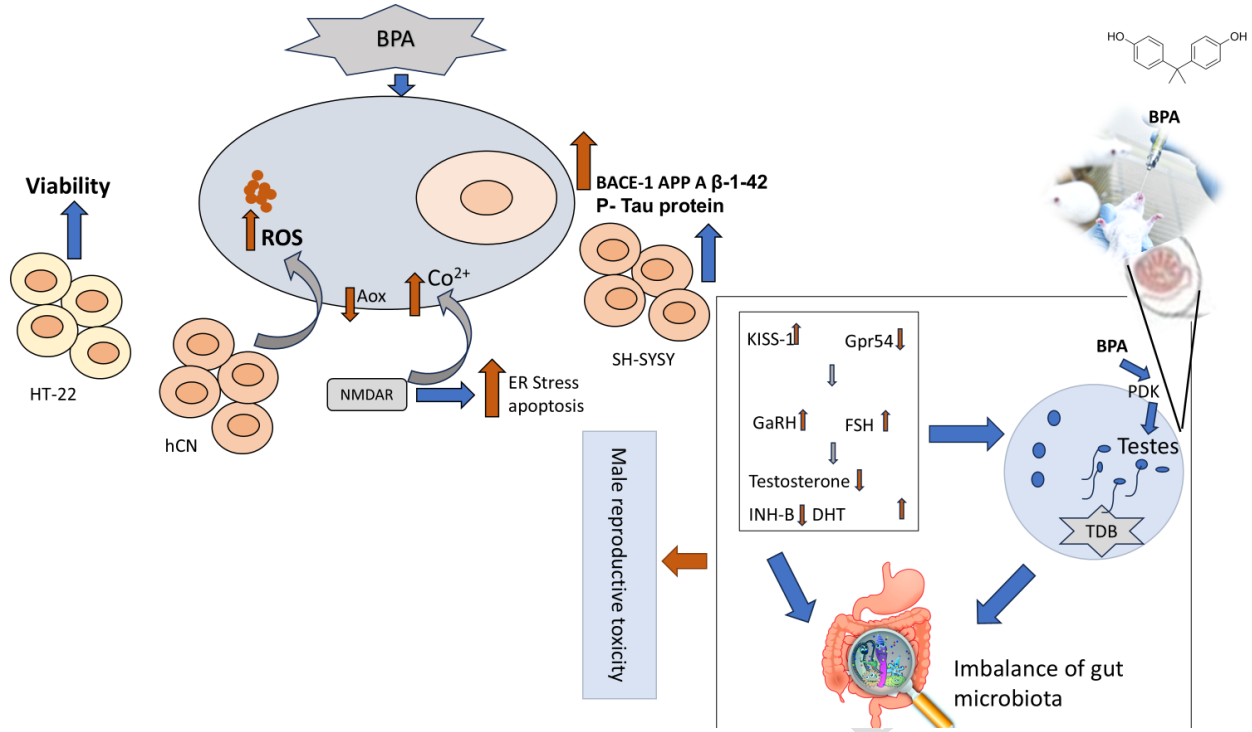

Fig 3.1: Mechanisms Connecting Reproductive Toxicity and BPA-Induced Oxidative Stress.

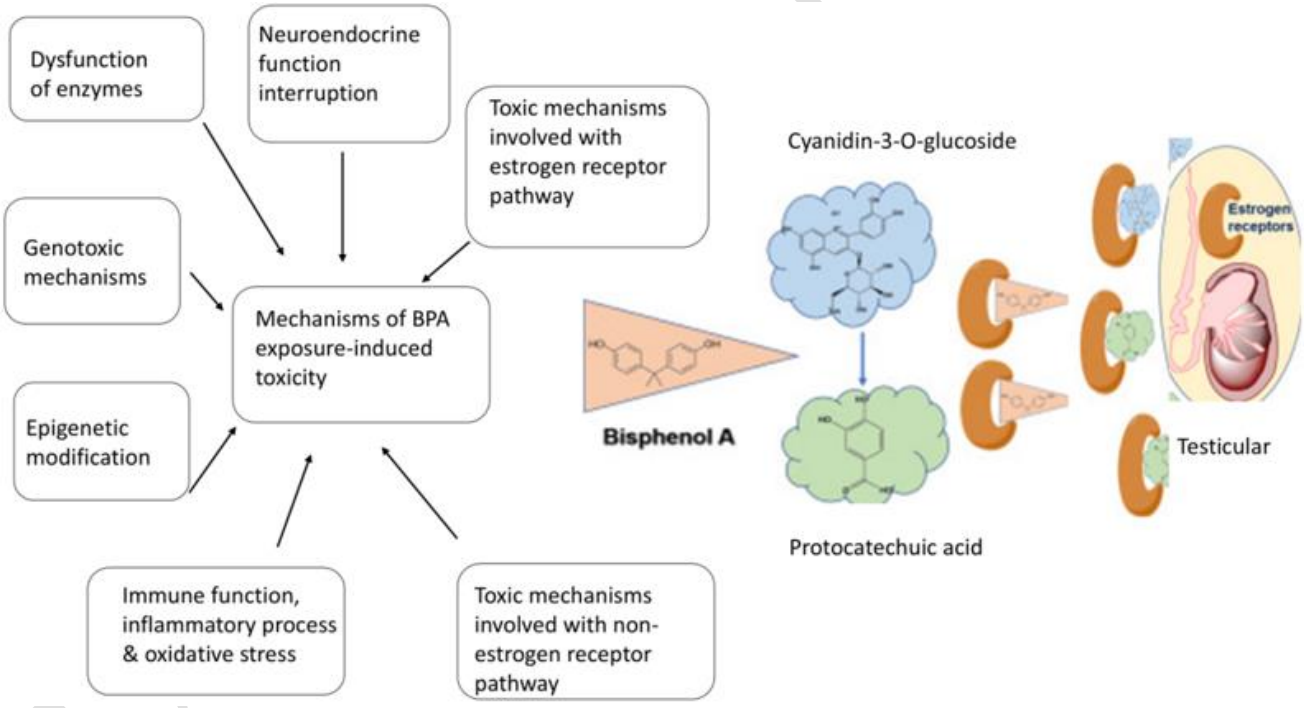

Fig 5.1: Protective Effects of Antioxidants on BPA Toxicity in Reproductive Systems.

Oxidative Stress as a BPA Toxicity Marker

Important for inflammatory responses, oxidative stress has been linked to immunological, cardio-metabolic, and aging disorders, neuro degeneration, and the onset and spread of cancer through a variety of unclear processes (Spahis, Borys, & Levy, 2017). For cells to remain healthy, develop, grow, and survive, the redox balance must be regulated (Y. Zhang et al., 2011). Superoxide anions, peroxides, and hydroxyl radicals (ROS) are produced by healthy cellular metabolism and are engaged in the well-regulated process of redox balancing (Kumar & Pandey, 2015). Important for inflammatory responses, oxidative stress has been linked to immunological, cardio-metabolic, and aging disorders, neuro degeneration, and the onset and spread of cancer through a variety of unclear processes (Vallese, Cordone, Pecorelli, & Valacchi, 2023). For cells to remain healthy, develop, grow, and survive, the redox balance must be regulated (Ursini, Maiorino, & Forman, 2016). Superoxide anions, peroxides, and hydroxyl radicals (ROS) are produced by healthy cellular metabolism and are engaged in the well-regulated BPA is a metabolic and endocrine disrupting chemical that can impair oxidative homeostasis

through direct or indirect mechanisms, such as increasing oxidative mediators and reducing antioxidant enzymes, determining mitochondrial dysfunction, changing cell signaling pathways, and inducing apoptosis (Ursini et al., 2016).

BPA induces oxidative stress by increasing lipid peroxidation and hydrogen peroxide in the kidney, brain, and testis of mice, and by decreasing antioxidant enzymes superoxide dismutase (SOD), catalase, glutathione reductase (GR), and glutathione peroxidase (GSH-Px) and decreasing antioxidant enzymes in the liver and epididymal sperm of rats ulated process of redox balancing (Kini, Kumar, Nayanatara, & Megha, 2024). The ROS increase induced by BPA has been reported in several cell types with concentrations ranging from non-molar to micro molar (Yin et al., 2017). Differences in ROS generation, duration, and cytotoxicity appear mainly based on the concentration of BPA, on cellular backgrounds, exposure time, and sensor fluorescent reagents (Huang et al., 2022). BPA has been recently associated with inflammation markers in addition to oxidative stress in humans Yang and colleagues previously carried out a cross-sectional investigation involving men and women going through menopause or post menopause (Choi, Ha, & Kim, 2017). They found that urinary BPA levels were positively correlated with urinary oxidative stress and blood inflammatory biomarkers (changes in white blood cell count and C-reactive protein) in women going through post menopause, suggesting that the effects of BPA vary depending on gender and hormonal status (Ferguson, Cantonwine, McElrath, Mukherjee, & Meeker, 2016). According to these scientists, the effect of BPA toxicity on gender could be attributed to receptor occupancy and estrogen levels (Sifakis et al., 2017). The ER expression is known to be age and gender related. Due to the extremely low hormone levels in postmenopausal women, xeno estrogen BPA can bind to the ER more extensively, which can cause harmful cellular reactions like inflammation and oxidative stress (Matarrese et al., 2021). Oxidative stress and inflammation have a well-established association; they are closely related to cellular functions and may be the causes or effects of cell damage (Keane, Cruzat, Carlessi, de Bittencourt Jr, & Newsholme, 2015). The production of reactive oxygen species (ROS) and nitrogen species by immune cells such as neutrophils and macrophages has a role in the development of chronic inflammation (Fialkow, Wang, & Downey, 2007). Widely regarded as potential biomarkers for oxidative stress, malondialdehyde (MDA) is a sign of lipid peroxidation, and 8-hydroxy-deoxyguanosine (8-OHdG) is a marker of DNA oxidation (Graille et al., 2020). Several investigations have shown their rise in BPA-exposed organisms (Ribeiro, de Melo Orfao, & Pereira, 2017). The vicious loop between inflammation and oxidative stress is maintained by numerous different redox-sensitive signal transduction pathways, including c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein (MAP) kinase, and transcription factor AP-1(Sarg et al., 2024).

BPA-induced oxidative stress has been linked to the cytotoxicity of human B cells [30], the suppression of immunological response in vitro in murine macrophages, and the impairment of immune response in animal models (Pirozzi et al., 2020). Additionally, exposure to BPA increases the expression of pro inflammatory cytokines in numerous tissues and organs (such as serum, the colon, the liver), as well as interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α) (Wang, Yin, & Zeng, 2019). Moreover, NOD-like receptor protein 3 (NLRP3) in acrosomes with inflammatory co-stimulus (i.e., nitric oxide) in adipocyte cells or the liver of BPA-exposed obese mice are activated in part by BPA-induced oxidative stress (S. Chen et al., 2023).

Mitochondrial impairment is one of the mechanisms of oxidative stress caused by BPA, behind lipid peroxidation and inflammatory reactions (Nagarajan, Maadurshni, & Manivannan, 2024). Low levels of BPA cause hepatic toxicity by affecting the liver's mitochondrial activity (Khan et al., 2016). Additionally, this pollution causes changes in the expression of genes related to mitochondrial activity and metabolism, ATP depletion, the release of cytochrome c, loss of mitochondrial mass and membrane potential, and mitochondrial metabolism (Sun et al., 2022). Sex differences in oxidative stress depend not only on the higher antioxidant defense in females but also on the increased generation of ROS in males (Tiberi et al., 2023). In fact, some studies have reported a gender-dependent NADPH oxidase activity, resulting in the excessive formation of reactive intermediates in male mice. Based on the intriguing literature concerning this issue, it will be relevant to carry out comparative studies on gender-related (Rosa & Flores, 2017).

Mechanisms Connecting Reproductive Toxicity and BPA-Induced Oxidative Stress

Males and Females have higher levels of reduced glutathione than males possess, and oxidative damage to mitochondrial DNA is lower in females than in males.

BPA Genetic Harm

The primary causes of genetic DNA damage are chromosomal abnormalities, which include aneuploidy, DNA strand breaks, DNA adducts, and gene mutation (Phillips & Arlt, 2009). Despite the fact that BPA is widely distributed and that people are constantly exposed to other contaminants when they are around, no information has been released regarding how BPA directly damages DNA by causing oxidative stress and the subsequent consequences this has on reproduction (Hengstler et al., 2011). Preclinical research conducted in vitro and in vivo has demonstrated that BPA induces mutations, aneuploidy, and DNA adduct formation (Tiwari et al., 2017). These changes could be a factor in the development of birth abnormalities, miscarriages, and infertility (Agenor & Bhattacharya, 2015). Additionally, BPA inhibits the base excision DNA repair mechanism that is brought on by laser irradiation (Gassman et al., 2015). The primary genetic abnormalities are chromosomal aberrations, which include aneuploidy, DNA strand breaks, DNA adducts, and gene mutation (Rejhová, Opattová, Čumová, Slíva, & Vodička, 2018). Through the generation of MDA, phenoxyl radicals, and ROS, BPA-induced DNA damage has been linked to oxidative stress. This can result in direct DNA changes that are amplified by the disruption of antioxidant enzyme pathways (Dehghani et al., 2023).

Table 1: Classification of Antioxidant Approaches Against BPA Toxicity on Male and Female Reproductive Systems

Classification	Type	Dose (Suggested Values)	Notes
	Glutathione + Vitamin E	10 µM + 5 mM	This combination counters BPA-induced oxidative damage and improves reproductive health in animal studies.
	Vitamin C + Vitamin E	100 mg/kg + 50 mg/kg	Co-administration enhances protection against oxidative damage in the ovaries and improves fertility.
Vitamins and Co-Factors	Vitamin E	6 mg/100 g bw	Supports testicular and sperm health, reducing BPA-induced apoptosis.
	1,25-Dihydroxyvitamin D_3 ($1,25D_3$)	0.2 µM	Mitigates mitochondrial DNA damage and supports reproductive tissue health.
	Coenzyme Q10	200 mg/L	Enhances ROS reduction and prevents mitochondrial dysfunction in BPA-exposed models.
	α-Lipoic Acid (LA)	30 mg/kg	Reduces oxidative stress and supports antioxidant enzyme activity.
Natural Antioxidants	Retinoic Acid	10 mg/kg	Improves oxidative balance and reduces BPA's estrogenic effects.
	Gallic Acid	40 mg/kg	Counters lipid peroxidation and oxidative stress due to chronic BPA exposure.
	Cordyceps Militaris Extract	300 mg/kg	Enhances antioxidant defenses and reduces oxidative stress markers in reproductive tissues.
	Cuscuta Chinensis Flavonoids (CCF)	60 mg/kg	Blocks transcription of apoptotic proteins, improving sperm quality and reducing ROS levels.
Hormones	Melatonin	15 mg/kg	Reduces ROS and lipid peroxidation, while protecting mitochondrial integrity in BPA-exposed cells.
	Selenium	0.7 mg/kg	Reduces ROS and improves antioxidant defense mechanisms in reproductive tissues.
Trace Elements	Selenomethionine	4 mg/kg	Prevents testicular toxicity and enhances antioxidant enzyme activity.
	Betaine	5 g/kg	Supports maternal and neonatal health, reducing oxidative stress during BPA exposure in gestation.
Methyl Donors	Vitamin B_{12} + Folic Acid	20 µg/kg + 20 mg/kg	Improves fetal development and reduces placental oxidative stress during gestation.

When Drosophila melanogaster was exposed to BPA through diet, found increased generation of reactive oxygen species (ROS) and lipid peroxidation, indicating impaired antioxidant function and mutagenesis consequences (Anet, Olakkaran, Purayil, & Puttaswamygowda, 2019). Furthermore, the BPA treatment increased ROS generation in pig embryos, which resulted in cytochrome c release, damage to the mitochondria and DNA, and apoptosis via the p53-p21 signaling pathways (Mathur et al., 2012). After BPA was exposed to rat ovaries ex vivo, Ganesan et al. observed that BPA alkylating metabolite also caused damage to DNA (Ganesan & Keating, 2016). Urinary BPA levels were found to be correlated with MDA and/or 8-OHdG in several human studies (Steffensen, 2020). BPA blood levels were found to positively correlate. Prostate epithelial cells also showed signs of BPA genotoxicity: following a 24-hour exposure to escalating doses, BPA suppressed p53 expression (Evans, 2022). The prostate cells treated with high or low concentrations of BPA had DNA adducts (De Flora et al., 2011).

The same authors also found that when male rats were exposed to BPA (200 mg/kg for 10 days), there was a noticeable increase in MDA and nuclear spreading factor in spermatozoa, which may indicate that these germ cells are fragile (Sadek et al., 2024). In spermatogonia (GC-1 cell line), micromolar BPA doses have been shown to cause ROS generation, DNA damage, and cytotoxicity. Remarkably, at non-cytotoxic micromolar and nanomolar doses, the induction of DNA strand breaks and its association with ROS production were also noted (Meli et al., 2020). Other cell lines, however, did not exhibit the induction of strand breakage by non-cytotoxic doses of BPA. The differing views about the genotoxic effects of BPA on DNA may be due to variations in BPA concentrations used, which are frequently higher than those found in ambient matrices. BPA causes genotoxic effects in somatic and germ cells when tested in vitro, but it cannot be regarded as a "true" genotoxic agent in vivo because it does not cause cancer in animals (Bariar, Vestal, & Richardson, 2013). It is unclear if BPA can have an indirect genotoxic effect in the context of other environmental contaminants or pathological circumstances, as it cannot induce genetic damage when present in environmental amounts (Langie et al., 2015).

Effects of BPA Epigenetics

With distinct patterns that change based on the kind of cell, epigenetic mechanisms control gene expression and cellular phenotypes without changing the nucleotide sequence of the genes (F. F. Chen, 2007). Numerous investigations have demonstrated the detrimental effects of epigenetic modifications and DNA damage on early embryonic development (Ornoy, Reece, Pavlinkova, Kappen, & Miller, 2015). The DNA methylation and histone modification patterns undergo significant programming and reprogramming throughout this time, and the epigenetic mechanisms can modify the male and female genomes in a tissue-specific manner through activation/deactivation processes (Navarro-Martín, Martyniuk, & Mennigen, 2020). Methylation limits the binding of transcription factors to DNA, which is crucial for mammalian development, or it induces gene silence by proteins involved in gene expression (Ehrlich & Lacey, 2013). According to published research, the epigenetic effects of BPA and other environmental contaminants on

reproduction vary based on the type of exposure (dose, duration, and route), the gender, and the stage of life (Mileva, Baker, Konkle, & Bielajew, 2014). BPA was given to female agouti yellow mice at a dose of 50 mg/kg by food, causes a DNA hypomethylation that results in phenotypic changes in the coat color of offspring (from the mating to the weaning stage) (Rosenfeld et al., 2013).

On the other hand, Doshi et al. found that BPA administration caused hypermethylation of estrogen receptor promoter regions in the testicles of newborn rats during the first five days of life, which interfered with spermatogenesis and reduced fertility (Cariati et al., 2020). BPA exposure, beginning at low concentrations, may influence both DNA hypermethylation and hypomethylation in CpG islands during fetal development and in a dose-dependent way (Onuzulu, Rotimi, & Rotimi, 2019). Contradictory findings from other studies indicate that BPA-induced epigenetic modifications have the opposite effect on DNA methylation; the underlying molecular and cellular mechanisms are yet unknown. Indeed, chromosomal disintegration with both DNA hypermethylation and hypomethylation has been linked to increased ROS generation and oxidative stress (Chianese et al., 2018). BPA has been shown to cause epigenetic reproductive harm, and oxidative stress and sperm epimutations may be epigenetically passed down to progeny through DNA methylation (Lombó, Fernández-Díez, González-Rojo, & Herráez, 2019). Oral exposure to BPA during gestation and/or lactation in pregnant albino rats resulted in increased MDA levels and DNA hypermethylation at CpG islands in the promoter genes of ERα and DNA methyltransferases in the testis of the male offspring (El Henafy, Ibrahim, Abd El Aziz, & Gouda, 2020). There was also a description of the decline in superoxide dismutase (SOD), GST, and GSH-Px levels (Chattopadhyay, Sahoo, Subudhi, & Chainy, 2007).

This data aligns with our unpublished findings about BPA-induced liver metabolic impairment in obese mice. The global DNA hypermethylation (% of methyl cytosine/total) brought on by high-fat diet is made worse in our experimental setting by a 21-day oral BPA exposure (50 µg/kg daily in corn oil) (Martos et al., 2017). According to an in vitro investigation, acute BPA caused aberrant cytoskeletons, lower maturation rates, elevated ROS generation, DNA methylation, and apoptosis/autophagy rates in pig oocytes (Sharma, Sharma, Gupta, & Srivastava, 2019).The authors came to the conclusion that BPA might cause additional disruptions to oocyte meiosis by altering the state of DNA methylation. After exposing pig embryonic-derived parthenoides to BPA, Guo et al. found that increased ROS production was linked to mitochondrial and DNA damage, which in turn caused autophagy and altered DNA methylation (decreasing 5-methyl-cytosine and DNA methyl transferase RNA) and may have an impact on the health of the offspring (Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). On the other hand, the impact of a subacute BPA exposure on an adult male minnow's testes, the rise in the generation of hydrogen peroxide antioxidants and the hyper methylation of DNA worldwide (Santiago, Moreno-Munoz, Quintero-Jiménez, Garcia-Torres, & Gonzalez-Redondo, 2021).

Metabolic and Endocrine Disruption

By changing hormone production and metabolism and binding to hormone receptors, endocrine disruptors can alter hormonal balance (Nadal, Quesada, Tuduri, Nogueiras, & Alonso-Magdalena, 2017). These changes can lead to a wide range of developmental and reproductive problems (Skakkebaek et al., 2016). Numerous studies conducted recently, including in vitro, in vivo, and epidemiological ones, have connected EDC exposure to a higher risk of developing a number of diseases, including obesity, metabolic syndrome, type 2 diabetes, and cardiovascular diseases (Lind, Ingvaldsen, & Furevik, 2018). In fact, some disruptors really cause metabolic illnesses directly, while others work by raising the disease's threshold or sensitivity (Casals-Casas & Desvergne, 2011). There is ample evidence that it is difficult to objectively evaluate the dangers associated with EDC exposure due to the variety of chemical structures and methods of action, as well as factors such as developmental stage, timing, and dose exposure (Fuhrman, Tal, & Arnon, 2015). BPA, mimics the structure and actions of 17-βestradiol; additionally, it binds to GPR30 and other conventional and non-classical membrane estrogen receptors (Molina-López et al., 2023). These activities cause various alterations in the ovary, mammary gland, and uterus organs that target estrogen in females exposed to BPA during pregnancy (Paulose, Speroni, Sonnenschein, & Soto, 2015).

Furthermore, BPA suppresses receptor degradation and ubiquitination by interfering with target gene transcription that is mediated by ERβ (Amir et al., 2021). Moreover, BPA functions as an antagonist by binding to the androgen receptor. It is well known that the androgen receptor plays a key regulatory role in androgen cell signaling and is crucial for the development and function of male reproduction (Perera et al., 2017). Together with thyroid hormone activity, the hypothalamic-pituitary-testicular axis regulates both human and animal spermatogenesis (La Vignera & Vita, 2018).The correlation between BPA exposure and lower levels of testosterone in Chinese men as well as higher serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (X. Liu et al., 2015). As is well known, FSH and LH promote testosterone synthesis and boost prostate growth by acting on Sertoli and Leydig cells, respectively (Ramaswamy & Weinbauer, 2014). According to a recent review, BPA has a negative impact on male reproductive hormones and has comparable effects on thyroid hormones, which are known to affect sperm production and male fertility (Cariati et al., 2020). Thyroid hormone levels were shown to be lowered in newborn girls exposed to BPA later in gestation, and thyroid illness may be associated with BPA-induced ROS generation (Mohammed et al., 2020).

The connection between BPA and metabolic illnesses (such as obesity and diabetes) can have an impact on both male and female fertility and reproduction by causing fat buildup and impairing the metabolism of fats and carbohydrates, which is linked to inflammation (Heindel et al., 2017). BPA is a lipophilic compound that builds up in fat, increasing the quantity and size of adipocytes and causing weight gain. BPA, as described before, modifies the release of adipokines at ambient levels by decreasing

anti-inflammatory adiponectin and increasing pro-inflammatory leptin and other inflammatory cytokines (e.g., IL-6, TNF-α) (Ahmed, 2020). It is well known that the relationship between energy balance and reproduction depends on adipokines like resistin and leptin as well as gastrointestinal peptides (Comninos, Jayasena, & Dhillo, 2014). Similar to insulin resistance, high levels of leptin are associated with fat mass and leptin resistance, which are common in obesity and related diseases such diabetes (Zimmet et al., 1999). It's interesting to note that people who have greater blood levels of BPA are more than twice more likely to acquire diabetes than people who have lower levels of BPA, and that risk increases with age (Hwang, Lee, & Bang, 2018).

Signaling Cell:(Zimmet, Boyko, Collier, & de Courten, 1999)

Depending on the type and function of the cell, BPA activates one or more distinct and numerous cell signaling pathways (Murata & Kang, 2018). In non-genomic signaling, BPA binds to GPR30 and mER, activating these receptors and triggering rapid estrogenic signaling that activates kinase systems, including phosphoinositide 3-kinases (PI3K), protein kinase-A (PKA), and MAPK (Ahmad et al., 2024). It also modifies intracellular calcium levels in cancer cells, cAMP, and protein kinase-C (PKC) (Kamp & Hell, 2000). According to a recent summary, spermatozoa exposed to BPA in vitro activate these receptors, which are linked to elevated ROS (Cariati et al., 2020). While ROS are necessary for optimal sperm activity at low levels, large amounts of ROS cause damage to cellular lipids, proteins, and DNA as well as adverse effects on sperm motility, mobility, and acrosome reaction (Dutta, Majzoub, & Agarwal, 2019). These changes quickly lead to increased ROS availability in the cytoplasm and activation of MAPK, PI3K, and PKA (Krylatov et al., 2018). Increased production of reactive oxygen species (ROS) leads to phosphorylation of sperm proteins in their tyrosine residues, which in turn causes functional modifications of coregulatory genes and proteins through transcriptional and translational pathways, hence predisposing cells to aberrant outcomes (Shah & Brownlee, 2016).

Hence, BPA may impair spermatozoa's complicated oxidative stress response, which may have an impact on their capacity to fertilize (Ryu et al., 2023). It has also been shown that BPA causes increased ROS and lipid peroxidation in various cell types (Huc, Lemarié, Guéraud, & Héliès-Toussaint, 2012). It had been reviewed that BPA affects many cell-signaling mechanisms and pathways extracellular signal-regulate kinases (ERK), JNK) involve dininflammation, immune response, cancer, brain, and reproductive function; the increase of calcium and ROS and the activation of ERK and JNK are implicated in BPA-induced apoptotic cell death Several studies have determined that EDC-induced oxidative stress can impair male fertility by disrupting the cell junctions among cell testis (Xiao et al., 2020). The pathways involved in BPA male reproductive toxicity, analyzing the pathophysiological role of MAPK and inflammatory cytokines and that of the PI3K/c-Src/ focal adhesion kinase signaling pathway (Wong, Boon-Itt, & Wong, 2011). The resulting alteration of intercellular junctions, via polarity proteins, leads to reproductive dysfunction such as reduced sperm count and reduced semen quality (Costa & Mercadal, 1995).

Oxidative Stress-Induced BPA Toxicity on Male and Female Reproduction

Many conflicting studies on the impact of BPA on male fertility were gathered between 2000 and 2010, although numerous additional recent findings have consistently shown that BPA has negative effects on both male and female reproductive processes (Mendiola et al., 2010). Transgenerational investigations have shown that BPA specifically affects spermatogenesis and sperm quality in males; it also affects ovary, embryo development, and egg cell quality in females (Rizzo, Bortolotti, Rizzo, & Schiuma, 2023). In addition to its direct effects on reproductive organs, BPA also affects the ability of the offspring to reproduce because of its ability to penetrate the blood brain barrier (Yahav et al., 2019). Reproductive function changes have a permanent impact on adult fertility, particularly if they happen while the reproductive organ is still developing in a fetus especially oxidative stress (Al-Gubory, Fowler, & Garrel, 2010). Numerous preliminary results have demonstrated the influence of perinatal BPA exposure on male spermatogenesis through various modes of action (Lombó et al., 2019).

That oral BPA exposure in gestational day (GD) dams enhanced generation of reactive oxygen species (ROS) and activated the apoptotic pathway in the testis of male offspring, as shown by histological alterations (Quan, Wang, Duan, Huang, & Yang, 2017). In addition to changing sperm quality and motility in adult male mice, BPA treatment in CD-1 dams (GD7–14) also affected oxidative balance. Additionally, impaired spermatogenesis was seen in progenies in a mouse model of chronic BPA exposure of dams throughout the entire gestational period and continuing the oral delivery to male pups until sexual maturation (Delbes et al., 2022).This impairment was linked to a decline in antioxidant defense as well as a decrease in the expression of sirtuin 1, a crucial ROS generation sensor (Singh et al., 2018). Data from very recently confirmed that male pups exposed to BPA at a young age developed oxidative stress in their testicular tissue (Sedha, Kumar, & Shukla, 2015). It was shown in this comparative study between prenatal, perinatal, and postnatal BPA exposure that BPA-related epigenetic modifications happen irrespective of temporal exposure (Kunysz, Mora-Janiszewska, & Darmochwał-Kolarz, 2021).

However, the level of BPA's harmful impact on oxidative balance varied with period of exposure, peaking during perinatal exposure (from pregnancy to nursing) (Varshavsky et al., 2020). Adult rats exposed to BPA experienced a dose-dependent increase in reactive oxygen species (ROS) (Babu, Uppu, Claville, & Uppu, 2013). Oxidative stress was linked to metabolic impairment (hyperglycemia and hyperinsulinemia) and reproductive damage, as evidenced by the testicular reduction of insulin receptor substrate-2 and glucose transporter-8, two important proteins involved in the metabolism of testosterone and spermatogenesis (Dias, Parente, Vasconcelos, & Dias, 2014). BPA caused a significant increase in lipid peroxidation in the epididymis, testis, and

immune cells (i.e., lymphocytes and bone marrow) of adult rats (Srivastava, Mansimov, & Salakhudinov, 2015). This increase is linked to sperm quality impairment and the induction of several antioxidant enzymes, including SOD, catalase, and non-enzymatic reduced glutathione (Micheli et al., 2016). In the testicles of offspring from dams exposed to BPA, Khalaf et al. also recently discovered elevated levels of H2O2, lipid peroxidation, and depletion of antioxidant defense mechanisms (Marcu, Keyser, Petrik, Fuhrimann, & Maree, 2023). BPA changed the shape of the seminiferous tubule epithelium, reduced gonadotropin discharges, increased ROS generation, and decreased the antioxidant activity of catalase and SOD enzymes during the early stages of puberty (Zahran, Elbahnaswy, Mamdouh, & El-Matbouli, 2021). The primary cause of sperm failure and male infertility in the testis is increased oxidative stress, which is brought on by persistent alterations to the redox balance (Barati, Nikzad, & Karimian, 2020). These alterations result in ROS overproduction and the weakening of antioxidant defense (de Haan et al., 2003). It is crucial to emphasize that BPA's reproductive toxicity to oxidative stress was explicitly addressed in the clinical investigations (Bameri et al., 2024).

Yet, given the significance of oxidative balance in the physiology of sperm, oxidative stress may be the primary harmful mechanism responsible for BPA's toxicity to the male reproductive system (Ryu et al., 2023).The main factor contributing to male infertility and sperm failure in the testis is elevated oxidative stress, which is caused by ongoing changes in the redox balance (Bisht, Faiq, Tolahunase, & Dada, 2017). The overproduction of ROS and the weakened antioxidant defense are the outcomes of these changes (de Haan et al., 2003). It is imperative to underline that the clinical studies specifically addressed BPA's reproductive toxicity to oxidative stress (Ahmad et al., 2024). Yet, given the role of oxidative balance in the physiology of sperm, oxidative stress may be the major damaging mechanism responsible for BPA's toxicity to the male reproductive system (De Toni et al., 2020).

Protective Effects of Antioxidants on BPA Toxicity in Reproductive System

Differently sourced chemicals known as antioxidants stop the oxidation or overproduction of reactive oxygen species (ROS) in cells and tissues, hence averting oxidative stress (Valko, Rhodes, Moncol, Izakovic, & Mazur, 2006). Many studies conducted in the past few decades have shown how antioxidants including gallic acid, lipoic acid, N-acetylcysteine, ginger extract, and vitamins C and E can protect or lessen the toxicity caused by BPA in a variety of organs (Li et al., 2022). The preservation of spermatozoa's quality, vitality, motility, and morphology is one of the benefits linked to antioxidant agent supplementation (Cilio et al., 2022). It's interesting to note that antioxidants maintain sperm motility and fertilization potential while reducing oxidative stress in spermatozoa during cryopreservation (Bansal & Bilaspuri, 2011). Here, we look at several antioxidant classes that, when taken singly or in combination, have been shown to be effective in reducing the harmful effects of BPA on the reproductive systems of both men and women (Santiago et al., 2021).

Vitamins and Co-Factors

It has been shown that vitamins C, E, and glutathione affect sperm function (Yousef, Abdallah, & Kamel, 2003). Specifically, these three drugs inhibited the excessive release of reactive oxygen species (ROS) and increased intracellular ATP synthesis in spermatozoa exposed to BPA, hence preventing motility loss and aberrant acrosome reactivity (Amaral et al., 2016).The primary cause of the reduction in spermatozoa motility and fertilizing competence is increased ROS and their metabolites, which damage cells irreversibly by interfering with their enzyme systems, DNA, lipids, and proteins. Vitamin E (2 mM) and glutathione (5 mM) mitigated the effects of BPA (100 µM) on impaired fertilization and early embryo development (Dattilo, Giuseppe, Ettore, & Ménézo, 2016). One of the main endogenous antioxidants, glutathione's recycling is influenced by vitamin C and E levels and vice versa (Bouayed & Bohn, 2010). In fact, ascorbic acid, or vitamin C, is an electron in addition to its scavenging action (Santos et al., 2022, In the ovaries of rats exposed to a high dose of BPA, the combination of vitamins C (50 mg/kg) and E (50 mg/kg), but not these vitamins alone, was also able to exhibit a protective effect in reducing apoptotic cell death (Bilgi et al., 2019). It is well known that male germ cells contain large levels of vitamin E, and that vitamin E is essential for controlling the lipid peroxidation that takes place in testicular microsomes and mitochondria (Ourique et al., 2016). There is proof that male fertility was enhanced by vitamin E (4 mg/100 g bw), which shielded testicular cells and epididymal sperm from the apoptosis caused by BPA exposure in Wistar rats (Justin Margret & Jain, 2024). Recent research has shown that 1, 25-dihydroxyvitamin D3 (1,25D3; 0.1 µM) can modify the harmful effects of BPA (10 µM) on oxidative stress, specifically on the dynamics and function of mitochondria in ovarian granulosa cells (Jain, Stevens, Margret, & Levine, 2024). Furthermore, 1,25D3 shielded the female ovary against BPA-induced mitochondrial DNA loss (P. Liu et al., 2023). It's interesting to note that women who have been exposed to BPA had lower serum vitamin D levels (Brennan, Lewis, Gordon, & Prichard, 2024). Coenzyme Q10 (CoQ10), among other vitamins, has the ability to restore fertility and mitigate the reproductive toxicity linked to BPA exposure (500µM) in the Caenorhabditis elegans germ line (C. F. D. Carneiro et al., 2023).

By reducing oxidative stress through the scavenging of ROS and free radicals, decreasing meiotic DNA double-strand breaks, and restoring mitochondrial activity, CoQ10 partially counteracted BPA-induced DNA damage (M. F. H. Carneiro & Colaiácovo, 2023). In the context of BPA-treated worms, CoQ10 supplementation resulted in a decrease in the number of aneuploid embryos and chromosome abnormalities in oocytes at diakinesis (Bradford, Schlaepfer, Lauenroth, & Palmquist, 2020). All prokaryotic and eukaryotic cell types contain the biological thiol LA, which plays a crucial function in mitochondrial damage and lowers oxidative stress while also raising the amounts of other antioxidants (Herrero et al., 2008). As a biofactor of energy metabolism, LA responds powerfully to reduce oxidative stress and free radicals (Andrés, Pérez de la Lastra, Juan, Plou, & Pérez-

Lebeña, 2024)It also prevents the decline in glutathione levels, restricts the production of lipid peroxides (LPOs), and restores the balance of antioxidant enzymes in the body (Marí, Morales, Colell, García-Ruiz, & Fernández-Checa, 2009). In male rats, prolonged BPA (10 mg/kg) administration resulted in testicular and mitochondrial oxidative stress (Anjum et al., 2011). To be more precise, LA boosted both enzymatic and non-enzymatic antioxidants of mitochondria, such as glutathione reducase and succinate dehydrogenase, malate dehydrogenase, isocitrate dehydrogenase, monoamine oxidase, and NADH dehydrogenase, and corrected BPA-altered activity of these essential mitochondrial enzymes (Bayliak, Gospodaryov, & Lushchak, 2023).

Ultimately, oral LA treatment (100 mg/kg) for 30 days during BPA exposure (25 mg/kg, per os) in female Wistar rats resulted in a reduction of ovarian oxidative damage, preventing nitrosative stress and lipid peroxidation, and even more in combination with vitamin E (20 mg/kg, per os) (M. F. H. Carneiro & Colaiácovo, 2023). Retaining retinoic acid, a metabolite of vitamin A, may also protect against oxidative stress damage was found to increase the expression of genes linked to antioxidants in mature buffalo oocytes cultured in vitro (Rakha et al., 2022). Furthermore, in both healthy and varicocele sperm, all-trans retinoic acid increased glutathione transferase and SOD activities while lowering reactive oxygen species and MDA levels, indicating that retinol increases the activity of antioxidant enzymes (Malivindi et al., 2018). According to Koda et al., adult ovariectomized rats supplemented with 5 mg/kg of all-trans retinoic acid per os greatly inhibited the rise in uterine weight caused by BPA (100 mg/kg), hence blocking the estrogenic activity of BPA (F. Amjad et al., 2021). It's interesting to note that vitamin A-containing pomegranate juice reduces sperm abnormalities and increases caudal sperm count in rats by preventing BPA-induced structural alterations in the epididymis whereas hepatic retinoids are necessary for BPA biotransformation and subsequent (Funk & March, 1897).

Natural Extracts and Products

Among several preventive or therapeutic methods, it is advisable to contemplate the utilization of natural substances like phytochemicals and herbs (Ahmad et al., 2024). Mostly found in plants, fruits (such as pineapple, banana, grapes, gallnuts, apples, and lemons), and vegetables, gallic acid is an apolyhydroxyphenolic molecule that can either be free or partially hydrolyzed tannin (Kang, Liu, Liu, Wu, & Li, 2018). This chemical has been shown to have antioxidant qualities, which are associated with scavenging ROS and reserving metal ions (Balogh, Illés, Székely, Forrai, & Gere, 2003). Gallic acid (20 mg/kg in maize oil) has recently been found to have a role in testicular oxidative stress in adult rats exposed to chronic BPA (10 mg/kg) (Ola-Davies & Olukole, 2018). These authors demonstrated that Gallic acid restored the BPA-altered parameters of antioxidant enzymes, reduced testicular lipid peroxidation (MDA, MPO), and normalized the gonadosomatic index (which is used to assess sexual maturity in connection to testicular development) (Gezer, Üstündağ, Kılıç Baygutalp, Erbaş, & Özkaraca, 2024). Cordyceps militaris is a fungus that is used in traditional Chinese medicine to treat impotence, seminal emission, and infertility (Bach et al., 2022). It exhibits a variety of biological activities, including an antioxidant impact because of its polysaccharide and cordycepin content (Jędrejko, Lazur, & Muszyńska, 2021).

The preventive effect of Cordyceps militaris extract (200–800 mg/kg) against the reproductive harm caused by BPA poisoning (200 mg/kg) in rats has been studied (Salim, Pangkahila, & Sriwidyani, 2023). The natural product's dose-related effect led to an increase in sperm count and motility, which were both affected by BPA (Sharma et al., 2019). It also reduced oxidative stress and the associated alterations in adipocyte function. GSH levels and antioxidant enzyme activity were found to be enhanced by these effects (Peris et al., 2019).The primary constituents of Chinese herbal medicine C.chinensis, called Cuscutachinensis flavonoids (CCF) have anti-abortive and antioxidant properties (Hajimehdipoor et al., 2012). It has been found recently that these flavonoids (40 mg/kg) can lessen the testicular cell apoptosis caused by BPA (5 mg/kg) (Zhao et al., 2023). This effect in male mouse offspring (F1) following contextual maternal exposure to BPA and flavonoids is directly linked to oxidative damage Specifically, in the testes of F1 mice collected at postnatal days 21 and 56, CCF inhibited the transcription and translation of apoptotic proteins (caspase 7 and 9), thereby minimizing structural damage and improving fertility (Udeochu et al., 2023). Recently, mice given BPA (1 mg/kg) orally showed protective effects from hydroethanolic Murrayakoenigii extract of leaves (200 mg/kg) (Kaur & Gupta, 2020).

Melatonin

Melatonin is a neuro-hormone that is mostly secreted from the pineal gland. It is generated from tryptophan and operates on the hypothalamic-pituitary-gonadal axis (Mocchegiani et al., 1994). Melatonin is engaged in various homeostatic processes, such as controlling reproduction, maintaining circadian rhythms, and maintaining redox balance (Megha et al., 2024). Numerous experimental and clinical investigations emphasizing the safety of melatonin have led to a significant increase in interest in this substance as an antioxidant (Ramos et al., 2021). In fact, melatonin functions as an inducer of antioxidant enzymes and a scavenger of various nitrogen and ROS species, such as hydroxyl radicals, peroxynitrite anions, and H_2O_2 transcription of an enzyme (Tan, Manchester, Terron, Flores, & Reiter, 2007). Because of its molecular makeup, melatonin can pass through cellular membranes and enter the cytosol, mitochondria, and nucleus, protecting DNA and enhancing signaling (Kopustinskiene & Bernatoniene, 2021). A prior study demonstrated the protective effect of melatonin (10 mg/kg, i.p.) on adult mice's interstitial mitochondrial damage caused by brief exposure to BPA (10 mg/kg) (Priego et al., 2021). Additionally, following a prolonged exposure, melatonin (10 mg/kg, i.p.) was shown to be able to reverse BPA (50 mg/kg)-induced oxidative damage and apoptosis in rats' testes and the change of epididymal sperm (Sahu & Verma, 2023).

Melatonin combined the anti-apoptotic effect on rat germ cells with its capacity to regulate cellular redox balance

(Abo El Gheit et al., 2022). In fact, melatonin decreased apoptosis by increasing the redox-sensitive and anti-apoptotic protein Bcl-2, and it also positively regulated glutathione, SOD, and catalase, as well as MDA levels and H2O2 output in the tissues and sperm (Lu et al., 2018). Due to its manipulation of blood testosterone levels, melatonin's protective action on spermatocyte meiosis and proper sperm quality and production is also strongly linked to its control of cellular redox balance (Loren et al., 2017). Since the effectiveness of melatonin supplementation was shown to affect DNA alterations, it has been established that the hormone (10 mg/kg) enhanced the genotoxicity potential of BPA (200 mg/kg), lowering the amount of damaged DNA in adult rats' male germ cells by suppressing oxidative stress (Mączka, Grabarczyk, & Wińska, 2022). Specifically, spermatocyte immunostaining revealed that the melatonin preventive action reduced DNA movement within germ cells and the formation of γH2AX, a hallmark of DNA double-strand breaks (Geesink & Meijer, 2017). Alongside this effect, melatonin-induced decreases in the levels of reactive chemicals thiobarbituric acid and elevations in SOD were observed (Essawy et al., 2025). The protective impact of melatonin on adrenal and prostate function in adult male rats exposed to oral BPA for two weeks (Olukole, Lanipekun, Ola-Davies, & Oke, 2019). Later, after mother exposure to various levels of BPA, further investigated the pertinent effect of melatonin (1 mg/kg) in shielding F1 adult rats against male reproductive damage (Tain & Hsu, 2024).

In addition to improving testicular SOD, GSH, and GPx activity, melatonin's antioxidant-protective effect on interstitial necrosis in testis (caused by BPA administration in utero) was linked to limiting germinal cell degeneration and recovering BPA-altered tubular and luminal diameter. The beneficial effects of melatonin (20 mg/kg) on the changes in epididymal structure and sperm quality brought on by long-term exposure to BPA (25 mg/kg) (Heidarizadi, Rashidi, Jalili, & Gholami, 2022). There have also been reports of BPA having negative effects on the female reproductive system (Matuszczak, Komarowska, Debek, & Hermanowicz, 2019). The mechanisms behind the deleterious effects of BPA (100 µg/kg bw per day for 7 days) on mice's oocyte quality (meiotic maturation and fertilization capacity) (Yahav et al., 2019). By lowering ROS levels and preventing oocyte apoptosis, the scientists found that oral melatonin (30 mg/kg bw per day for seven days) increased the in vitro fertilization rate and restored BPA-induced changes to fertilization proteins and processes (M. Zhang et al., 2017). Additionally, melatonin guards against BPA-induced uterine deterioration (Bameri et al., 2024).

Selenium

The selenium plays a crucial function in reducing spermatogenic oxidative damage and apoptosis as well as preserving male fertility after BPA administration (Sahu & Verma, 2023). Consequently, selenium's capacity to regulate the crucial balance between germ cell death and proliferation during apoptosis in spermatogenesis has been previously proven (Yan et al., 2024). Selenium supplementation in the diet (0.5 mg/kg diet) decreased ROS and lipid peroxidation in mouse testes and ameliorated histopathological abnormalities, conserving basement membrane and lowering germ cell vacuolization in mice exposed to BPA (150 mg/kg) (Mondal & Bandyopadhyay, 2024). The interaction between selenium and selenoproteins, such as the ROS-interacting enzyme GSH-Px, is most likely the cause of this impact (Salvador, Barros, Da Luz, Piekarski, & de Francisco, 2020). In male rats exposed to 150 mg/kg of BPA, a recent study verified the protective effects of selenium (3 mg/kg) and nanoselenium (2 mg/kg) against reproductive damage. The selenium nanoparticle known as nanoselenium has lower toxicity, more surface activity, and better bioavailability than regular selenium (Zhou et al., 2019). Both elements have been shown to have a protective effect against BPA-induced testicular toxicity in rats; they also improved oxidative stress biomarkers, DNA fragmentation damage, inflammation, and the expression of particular spermatogenesis-related genes (Khalaf, Ahmed, Moselhy, Abdel-Halim, & Ibrahim, 2019).

Methyl Donors

Rats' BPA-induced unfavorable metabolic impact and oxidative stress were discovered to be improved, among other therapeutic techniques, by treating N-acetylcysteine (Elswefy, Abdallah, Wahba, Hasan, & Atteia, 2020). In the sulfation cycle, cysteine participates by serving as a donor of sulfur and a methyl donor during the conversion of homocysteine (Hcy) to methionine (Elswefy et al., 2020). Auto-oxidation of hcy produces reactive oxygen species (ROS) and may be involved in the beginning of reproductive problems. Hcy induces intrauterine abortion, premature birth, and low birth weight offspring when it is present in high amounts in the serum of pregnant women (Cetin, Berti, & Calabrese, 2010). Supplementing the diet of their offspring with methyl donors at doses capable of lowering hemoglobin levels in plasma alleviated intestinal digestion and absorption disorders brought on by BPA, which may be linked to DNA methylation (Mączka et al., 2022). Sows have shown that supplementing with vitamin B9, B6, B12, and betaine lowers plasma Hcy levels and improves reproductive function (Rizzo et al., 2023).

Consistent with these results, have recently shown that methyl donor supplementation in the mother's diet (3 g/kg betaine, 400 mg/kg choline, 150 µg/kg vitamin B12, and 15 mg/kg folic acid) during gestation effectively counteracted oxidative stress caused by BPA in the placenta and helped to maintain a healthy redox environment in the pig offspring as well as the fetus (Mou et al., 2018). The detrimental effects of BPA on placental integrity were actually mitigated by a dietary methyl donor, which also increased the antioxidant activity of enzymes (SOD, catalase, and GSH-Px) acting on placental trophoblastic cells and umbilical cord blood (Feng et al., 2023). These findings then had an impact on the maintenance of the redox balance in newborn piglets. It's interesting to note that how mother nutrition affected the properties of the muscles in the offspring following prenatal BPA exposure and co-treatment with methyl donors (Acharyya, 2007). BPA decreased methylation at the LDH promoter and increased the activity of the enzyme lactate dehydrogenase (LDH) as well as the amount of mRNA in the thoracic muscle at birth and during the finishing period (Ghimire et al., 2022). Through DNA methylation, the protective treatment with

methyl donors has long-lasting effects on the quality of hog flesh by influencing the expression of glutathione and LDH (Nordberg, Rinne, Kadir, & Långström, 2010).

Conclusions

Because BPA interferes with metabolism and endocrine function and has been linked to human diseases like cancer, diabetes, obesity, and reproductive issues, it has become a focus of significant investigation. This review offers a paradigm for comprehending how the pleiotropic reproductive deleterious effects following BPA exposure may be facilitated by the production of oxidative stress. Male reproductive organs are more susceptible to BPA exposure than female reproductive organs, according to multiple researches that have been reviewed. Research indicates that men may be more vulnerable for a number of reasons: (i) gender differences in glutathione levels and their relevance for the detoxification process (males have lower glutathione availability); (ii) females have a greater capacity for sulfate-based detoxification; (iii) male reproductive organs have a greater inflammatory response; and (iv) females are less vulnerable to oxidative stress.

BPA exposure during infancy and development can cause oxidative stress and lipid peroxidation, which can affect hormonal and metabolic processes in the reproductive system and be conserved in both humans and animal species. Inflammation will often arise and intensify oxidative stress, and vice versa. Oxidative stress is frequently the initial anomaly in an organ. Growing and convincing evidence indicates that a wide range of BPA doses or concentrations (in vivo and in vitro or human exposure) promote ROS generation and alter redox balance, inducing mitochondrial dysfunction and the modulation of cell signaling pathways related to oxidative stress, despite differences among doses, duration, model systems, and measured outcomes. In addition to its endocrine and metabolic disrupting qualities, BPA can also generate oxidative stress, which can act in a dependent or independent manner.

This can have significant effects on reproduction throughout prenatal, perinatal, and postnatal exposure, as well as in adulthood. However, when BPA exposure is coupled with additional risk factors including a poor diet, impaired metabolism, and coexisting disorders, the effects can be quite severe. Various antioxidant strategies have been found to date to mitigate BPA-induced harm to the reproductive systems of men and women. By lowering certain oxidative stress markers, lipid peroxidation, or DNA damage, and reestablishing the antioxidant defense, these substances increase both male and female fertility. To determine the specific molecular processes underlying these antioxidant compounds' protective effect on oxidative stress and inflammation which are responsible for the systemic and organ-specific toxicity of this ubiquitous xenobiotic new experimental and clinical research are necessary. More research on antioxidants is required to determine the best dosage and course of action for addressing BPA poisoning as well as to better characterize their value in a number of gender-dependent reproductive dysfunctions.

Author Contribution

AN and NW: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing—original draft, Writing - review and editing: NA, NA and SR: Data curation, Formal analysis, Investigation, Writing—original draft, Writing—review and editing.

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Availability of Data and Material

All the data is available and can be obtained on reasonable request from the corresponding author

Consent to Participate

All the authors equally participated in this research.

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