SHORT REVIEW ON PROTECTIVE EFFECTS OF POLYPHENOLS AGAINST DISORDERs CAUSED BY BISPHENOLS

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ABSTRACT

Endocrine-disrupting chemicals (EDCs) have recently attracted the interest of public health organizations, motivating substantial research to identify their effect on human health. Dysfunctions in endocrine system activities can raise the risk of a wide range of disorders, including cardiovascular disease, type 2 diabetes, cancer, and reproductive disorders. Given that bisphenol A (BPA) and other bisphenols are considered to raise the risk of these disorders primarily through activating oxidative and inflammatory pathways, it has been hypothesized that dietary substances with anti-inflammatory and antioxidant capabilities may mitigate their negative effects. Polyphenols have been analyzed for their capacity to protect against the negative effects of BPA and phthalates since they are some of the most well-established substances with such properties. Given the importance of defining the relationship between bisphenols and human health and discovering approaches to combat the harmful effects they may cause, this review will summarize the evidence on dietary exposure to bisphenols, how they influence disease risk, the basis for and available research on how polyphenols mitigate their adverse effects, gaps in knowledge, and future research suggestions.

Keywords: antioxidants, bisphenols, BPA, polyphenols

INTRODUCTION

Over the last few decades, the production and consumption of plastics have increased significantly. Despite appearing to be a seemingly perfect answer to technological difficulties in many industries, and a considerable advance in the ease and comfort of our lives, they are showing to be a serious threat to health and the environment after several years of exposition (Grob et al., 2019; Zwierello et al., 2020). Exogenous molecules that interact with the endocrine system and cause harmful effects in organisms are known as endocrine-disrupting chemicals (EDCs), sometimes known as environmental hormones. Out of a wide range of EDCs, bisphenol A (BPA) is the most common in the environment (Smith et al., 2020). In studies undertaken in Europe and the United States, detectable levels of BPA were found in more than 90% of urine samples from the general population (Becker et al., 2009; Calafat et al., 2008; Casas et al., 2011). Polyphenols are among the most abundant and widely distributed compounds in plants (D’Archivio et al., 2007). There are over 8000 distinct compounds in this group, with flavonoids accounting for more than half of them. They play a significant role in human nutrition on a daily basis. The potential of polyphenolic chemicals to prevent disease is thought to be owing to their ability to reduce the amounts of reactive oxygen species (ROS) in cells (Akhlighi et al., 2009). Polyphenols’ antioxidant activity might be direct, as a result of interactions with free radicals and their subsequent elimination (polyphenols operate as “scavengers” of free radicals), or indirect, as a result of metal ion chelation. It could also be indirect, due to these chemicals’ ability to modulate oxidative stress enzyme activity, increase the expression of genes encoding antioxidant enzymes, or defend against other antioxidants such as vitamin C and α-tocopherol (Pandey et al., 2009). Polyphenolic compounds have shown promise in preventing infections, cardiovascular and neurological diseases, diabetes, allergies, premature aging, cancer, and metabolic disorders induced by compounds released from plastics (Zwierello et al., 2020). Further study on the significance of polyphenols in mitigating the effects of bisphenols is necessary due to their biological and chemical properties, their ubiquity in the plant component of a diet, and their protective action against several xenobiotics. To date, an insufficient number of studies have been conducted to evaluate the effect of bisphenols and polyphenols on the organism, therefore the purpose of this review was to assess the potential protective effect of polyphenols against toxicity induced by bisphenols.

Bisphenols

Sources of exposure

Bisphenol A (BPA, 2,2-bis(4-hydroxyphenyl)propane), is a primary substrate in the manufacture of polycarbonate plastics, epoxy and polyester resins, and thermal paper (Lorber et al., 2015; Zwierello et al., 2020). As a result, BPA can be found in plastic food and beverage containers, cans, compact discs, personal protection equipment, sports equipment, medical materials such as dental fillings and composites, protective coatings on metal food containers, toys, and receipts. Exposure to endocrine disruptive chemicals, especially bisphenols, occurs primarily through the diet, in addition to the environment (Madore et al., 2022).

Metabolism

BPA is mostly absorbed through the gastrointestinal system, although it is also absorbed through the skin to a certain amount (Reale et al., 2021). BPA is metabolized in both the liver and the gut, where the microbiota regulates its metabolism to some extent (Wang et al., 2018). BPA is primarily transformed by glucuronorination by UDP-glucuronoyltransferase 2B15 (UGT2B15) and, to a lesser amount, sulfation by sulfotransferases 1A1 (SULT1A1) and 1A3/4 (SULT1A3/4) (Bucher et al., 2017; Völkel et al., 2002). These metabolites are quickly excreted from the body, but they are also susceptible to reversal processes mediated by β-glucuronidase (GUSB) and steroid sulfatase (STS). Cytochrome P450 enzymes cytochrome P450 family 2 subfamily C member 9 (CYP2C9), cytochrome P450 family 2 subfamily C member 18 (CYP2C18), and cytochrome P450 family 2 subfamily C member 19 (CYP2C19) oxidize a part of BPA to a catechol derivative, which can then be converted to o-quinones (with genotoxic activity) (Zwierello et al., 2020).

Toxic effects

BPA exposure impairs the liver, kidneys, neurological, reproductive, and hormonal systems. Some evidence suggests that BPA may potentially contribute to breast, prostate, and liver cancer, as well as neurodegenerative disorders (Caporossi et al., 2017; Rochester, 2013; Seachrist et al., 2016; Zwierello et al., 2020). Rahman et al. (2021) outlined many confounding factors that may be directly or indirectly related to human BPA exposure, as well as the differences between scientifically generated safe BPA dosages and those deemed “safe” by government regulatory authorities (Rahman et al., 2021). BPA exposure during early
development has been linked to the development of obesity (Engin et al., 2021; Lee et al., 2021; Moon et al., 2021), metabolic syndrome, type 2 diabetes (Lee et al., 2021; Rancière et al., 2019), and cardiovascular disorders (Lee et al., 2021; Shu et al., 2019). After oral intake of BPA, toxicokinetic investigations on laboratory animals and humans show similar outcomes: BPA is rapidly absorbed from the gastrointestinal tract and undergoes first-pass conjugation to the physiologically inactive metabolites BPA-gluconuride (BPA-gluc) and BPA-sulfate (Churchwell et al., 2014; Doerge et al., 2010, 2011; Shih et al., 2021). Human investigations following oral intake of BPA or a high-BPA diet are consistent. The goal of this study is to determine what extent unbound BPA exposure is reduced after oral exposure and that BPA-gluc is the predominant metabolite (ESFA, 2015; Shih et al., 2021; Teeguarden et al., 2011, 2015; Thayer et al., 2015; Vökel et al., 2002, 2008). BPA interacts with estrogen receptors and operates as either an agonist or antagonist via estrogen receptor-dependent signaling pathways according to its phenolic nature (Adgeoke et al., 2020).

The developmental origins of health and disease (DOHaD) theory (Tain et al., 2017, 2018) has been established in numerous studies, highlighting the connections between the periconceptional, fetal, and early infant phases of life and the eventual development of adult obesity and related metabolic diseases (Lacagnina, 2020). BPA's lipophilicity allows it to pass across placental and blood-brain barriers into the fetus, where it causes oxidative damage and nerve injury, disrupting brain development and causing lasting fetal brain disorder (Mhaouty-Kodja et al., 2018). Obesity is undoubtedly exacerbated by poor diet and lack of exercise, but recent research has identified an estrogen endocrine disruptor chemical BPA as a chemical that may act as an environmental obesogen and either directly or indirectly impact fat accrual, explaining how it might be involved in sex hormones, genomic and non-genomic pathway involving nuclear estrogen receptors, differing developmental pattern and/or epigenetic influence (Janesick et al., 2012; Shih et al., 2021).

Many of the disorders associated with endocrine disruptors are the result of an oxidative stress and inflammatory pathways (Nediani and Giovannelli, 2020). Inflammation and oxidative stress function together to reduce cellular antioxidant capability, allowing for free radical overproduction. These free radicals subsequently react with DNA and cell membranes, causing irreversible damage and creating toxic compounds that promote the progression of chronic disease (Khanarsi et al., 2009). Thus, diets high in antioxidant/anti-inflammatory chemicals may mitigate some of the health hazards associated with EDCs by decreasing inflammatory reactions and neutralizing free radicals (Madore et al., 2022).

Polyphenols

Antimicrobial, antioxidant, and anti-inflammatory properties of dietary polyphenols from regularly consumed foods and beverages, as well as herbs and botanicals, are well documented. Dietary polyphenols can be divided into a variety of categories. Tannins, flavonoids, and lignin-carbohydrate complexes, all of which have been linked to antimicrobial and anti-inflammatory characteristics in mechanistic investigations, as well as those that are routinely taken as dietary sources, fall into this category. 437 polyphenol chemicals were identified in raw and cooked meals in a newly built database for European countries (Basu et al., 2016; Nair et al., 2018; Shih et al., 2021). Dietary flavonoids and their subclasses (anthocyanidins, flavones, flavan-3-ols, flavonols, and flavanones) have been extensively researched for their connections to chronic disorders, including inflammation (Basu et al., 2018; Cassidy et al., 2013; Gao et al., 2012; Wedick et al., 2012). Over the last decade, epidemiological and clinical studies have accumulated substantial evidence linking dietary polyphenol intake, particularly flavonoids found in fruits, tea, and olives, to a risk of several chronic diseases (Pandey et al., 2009), including diabetes (Zhao et al., 2016), cardiovascular diseases (Gao et al., 2012), cancer (Rydén et al., 2016), and neurodegenerative diseases (Wedick et al., 2012).

In vivo studies

Rats were exposed to BPA during the perinatal period to determine the effects of RBE (Resveratrol Butyrate Esters) supplementation on obesity-related indicators and intestinal microbiota in their female offspring to better understand the potential applications of RBE. RBE supplementation was found to reduce BPA-induced weight gain and body fat formation, improve blood lipid-related marker concentrations, decrease the Firmicutes/Bacteroidetes ratio and Lactobacillus abundance, and increase Muribaculaceae abundance. RBE supplementation has the ability to influence the intestinal levels of acetate in female offspring rats. RBE induced changes beyond regulation of microbial abundance and function but also had a modulatory action in the intestinal microbiota, implying that it could be employed in pratomatological research (Shih et al., 2021).

According to Liao et al. (2021), RBE significantly reduced BPA-induced oxidative damage in the liver, decreased ALT (alanine transaminase) and AST (aspartate transaminase) activities, and significantly elevated mRNA expression and antioxidant enzyme activities, enhancing liver function and minimizing oxidative damage in the livers of offspring rats. Tissue staining revealed convincing evidence of BPA-induced liver damage, which was minimized by RBE therapy. Their findings also show that after maternal rats ingested BPA, their offspring’s gut microbiota distribution was altered, reducing intestinal barrier function and inducing inflammatory reactions and oxidative damage in their livers. RBE, on the other hand, reversed the abundance of Muribaculaceae and Adlercreutzia in the liver and the concentration of butyric acid in the gut, suggesting both reparative and neuroprotective effects on colonic epithelial cells. These findings suggest that RBE could be used to develop liver-protecting medications that protect against BPA-induced oxidative damage (Liao et al., 2021).

Bordbar et al. (2021) conducted experiments to determine the liver-protective effects of RES (resveratrol) in BPA-exposed rats. In the BPA group, the number of hepatocytes, total liver volume, and hepatocyte nucleus and cytoplasm volumes all decreased by 41% (P<0.001), 18% (P<0.001), 32% (P=0.030), and 37% (P=0.014), respectively. The number of Kupffer cells (KCs) and the length of sinusoids were increased in the RES group with BPA exposure. They noted a significant histological examination revealed vacuolization, sinusoidal space dilatation, and congestion in the BPA group. To summarize, the overall volume and length of sinusoids, as well as the number of KCs, were smaller in the RES group than in the BPA group in their study. Furthermore, after oral administration, the RES group showed an increase in total liver volume, hepatocyte nucleus and cytoplasm volumes, portal triad sizes, and hemorrhage counts (Bordbar et al., 2021).

Another study investigated the effects of a methanol extract of Vaccinium arnottianum (VAM) on BPA-induced testicular toxicity in male Sprague Dawley rats. When VAM was combined with BPA to treat testicular toxicity, it restored natural antioxidant enzymes, DNA damage in the testes, and hormone levels in the testes. The inclusion of BPA greatly supported the ability of VAM in the presence of oxidative stress-induced testicular injury. The inclusion of phenolics and flavonoids (ferulic and vanillic acid), lycopene, beta-carotene, and alkaloids in VAM may explain its anti-inflammatory effect (Zahra et al., 2020).

Another in vivo study was conducted to investigate the effect of grape seed extract (GSE) and resveratrol on the abundance of Muribaculaceae and Adlercreutzia. The rats were randomly separated into groups and given GSE (3 and 10 mg/kg/day i.p.), resveratrol (100 mg/kg/day i.p.), BPA (35 mg/kg/day, gavage), BPA plus GSE (3, 6, and 12 mg/kg/day i.p.), BPA plus resveratrol (25, 50, and 100 mg/kg/day i.p.), and BPA plus vitamin E (200 IU/kg every other day). After 2 months, contractile and relaxation responses on the isolated aorta were evaluated. BPA increased malondialdehyde levels in the aorta (p < 0.001) while decreasing vascular responses to potassium chloride (p<0.01), phenylephrine (p < 0.001), and acetylcholine (p < 0.01). GSE and resveratrol's high antioxidant capacities may explain their protective role against BPA endothelial impairment (Bordbar et al., 2021).

According to Ramesh et al. (2019), BPA (35 mg/kg/day, gavage, 2 months) exhibited negative effects on blood pressure, hepatic expression of ATP Binding Cassette Subfamily G Member 5 (ABCG5) and ATP Binding Cassette Subfamily G Member 8 (ABCG8), and lipid profile. Furthermore, chronic BPA exposure decreased paraoxonase-1 (PON1) serum levels while raising leptin, adiponectin, and body fat index serum levels. Raising fasting blood sugar (FBS), serum insulin levels, and the PAkt/Akt and pPI3K/P13K ratios in the liver, impeded insulin signaling; GSE (3 mg/kg*day i.p., 2 months) and resveratrol (25 mg/kg*day i.p., 2 months) may protect against BPA-induced metabolic abnormalities, according to their study. Similarly, being a potent antioxidant, vitamin E (200 IU/kg every other day) reversed BPA-induced oxidative stress parameters. The protective effects of GSE and resveratrol may be related to their effects on hepatic ATP Binding Cassette Subfamily G Member 8 (ABCG8) expression, enhanced insulin signaling, and antioxidant capacities. GSE and resveratrol are suggested as adjuvant treatments for metabolic disorders induced by toxins or medications (Ramesh et al., 2019).

Fouda et al. (2021) investigated the potential therapeutic effects of mesenchymal stem cells (MSCs) and resveratrol in a rat experimental model after Bisphenol-A evident uterine damage. According to the findings, BPA induced significant changes in endometrial tissue, including inflammatory cell infiltration, blood extravasation, collagen fiber increase, PAS staining decrease, and Transforming growth factor (TGF-1) immunoreactivity increase. BPA also elevated oxidative stress markers such as malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and apoptosis-related genes (Fouda et al., 2021).

BPA significantly altered blood gonadal hormone levels, including an increase in follicle-stimulating hormone (FSH) and a decrease in estradiol (E2) and progesterone (P). After treatment with resveratrol, MSCs, or a combination of the two, histological findings improved significantly, gonadal hormones were restored to relatively physiological levels, and oxidative stress markers and apoptotic genes were significantly reduced. In terms of the parameters studied, combination therapy with resveratrol and MSCs demonstrated more significant therapeutic effects than either MSCs or resveratrol alone (Fouda et al., 2021).

Essawy et al. (2021) determined the therapeutic effects of asagaloide IV (ASIV) and Astragalus spinosus (A. spinosus) saponins against bisphenol A-induced neurotoxicity and DNA damage in juvenile PND20 (pre-weaning; age of 20 days) male Sprague Dawley rats. In the brain areas of BPA-treated rats, they observed an increase in oxidative stress and reduced catalase (CAT) and glutathione peroxidase (Glu), glutaminase (GA), and glutamine synthetase (GS). Co-administration of ASIV or A. spinosus saponin with BPA, on the other hand, significantly increased
concentrations of these neurochemicals. The current study also discovered that the levels of brain-derived neurotrophic factor (BDNF) and N-methyl-D-aspartate receptors (NR2A and NR2B) gene expression were restored in the BA+ASIV and BA+AV groups. Co-treatment of the BA group with ASIV or A. spinosus saponins considerably reduced the levels of reactive oxygen species (ROS) as well as the intensity of estrogen receptors (ERs) immunoactive cells and improved the histological abnormalities caused by BPA in several brain regions. According to their findings, ASIV or A. spinosus saponins may have a potential role in modulating the neurotoxicity and DNA damage caused by BPA (Essawy et al., 2021).

In vitro studies

The objective of the Çığ and Yıldızhan (2020) study was to determine the mechanism by which the antioxidative resveratrol affected Transient Receptor Potential Cation Channel Subfamily M Member 2 (TRPM2)-induced oxidative stress in duct principal mpkCCD34 cells induced by BPA exposure. Cells were divided into four groups: control and three experimental where medium was supplemented with resveratrol (50 μM for 24 h), BPA (100 μM for 24 h), and BPA + RES (in the previously mentioned concentrations). Intracellular free Ca2+ concentrations and TRPM2 channel currents were increased in BPA-treated cells but decreased after resveratrol treatment. BPA-induced mitochondrial membrane depolarization, (ROS), caspase 3, caspase 9, and apoptosis were all reduced by the resveratrol treatment. Finally, resveratrol protected cells from BPA-induced oxidative damage. In this study, the TRPM2 channel is demonstrated to mediate the protective effect of resveratrol (Çığ et al., 2020).

Grape seed extract (GSE) and resveratrol were investigated in vitro for their ability to protect against Bisphenol A-induced vascular damage. GSE and resveratrol were administered to human umbilical vein endothelial cells (HUVECs) in varying concentrations. After BPA was administered to the cells, the cell viability and effects on the protein level of cell adhesion molecules were examined using MTT assay and western blotting. In HUVECs, BPA (IC50: 220 μM) increased vascular cell adhesion molecule (p=0.05) and cleaved caspase3 (p=0.001) protein levels. Cotreatment with GSE, resveratrol, and vitamin E reduced the deleterious effects of BPA at some concentrations. BPA's vascular toxicity has been linked to lipid peroxidation and vascular toxicity. GSE and resveratrol's high antioxidant capacities may explain their protective role against BPA endothelial dysfunction (Rameshbrad et al., 2018).

During a 2019 study, the antioxidant efficiency of gallic acid (GA), a polyphenol molecule derived from plants, against various toxins generated oxidative stress was successfully demonstrated. The findings from this study suggest that GA may protect mitochondria isolated from rat liver from BPA-induced damage in vitro, most likely by inhibiting BPA-induced oxidative stress, mitochondrial amino acids, increasing the content of reduced glutathione, mitochondrial DNA damage, decreasing the levels of mitochondrial lipid peroxidation (LPO) and protein carbonyl (PCO), preventing changes in the activities of the Krebs cycle and respiratory chain enzymes, and preventing mitochondrial DNA damage (Dutta et al., 2019).

CONCLUSION

Despite the undeniable significance of polyphenols in preventing diseases induced by bisphenol, few studies were conducted on the topic. Future research should focus on the detailed mechanism of action of the effect of bisphenols and the antagonist effect of polyphenols. Furthermore, the function of high polyphenol concentrations should be explored in a pathologic context.

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