JMBFS

Journal of Microbiology, Biotechnology and Food Sciences

International peer-reviewed scientific online journal

Published by Faculty of Biotechnology and Food Sciences

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

Nikola Knizatova[*1], Hana Greifova[1], Katarina Tokarova[1], Tomas Jambor[1], Peter Massanyi[1], Adriana Kolesarova[1], Anton Kovacik[1], Norbert Lukac[1]*

Address(es): Ing. Nikola Knizatova PhD.,
[1] Slovak University of Agriculture, Faculty of Biotechnology and Food Sciences, Institute of Applied Biology, Trieda A. Hlinku 2, 949 76 Nitra, Slovak Republic, phone number: +421-37-6414896.

*Corresponding author: nikola.knizatova@uniag.sk

https://doi.org/10.55251/jmbfs.9475

ARTICLE INFO

Received 21. 9. 2022
Revised 3. 11. 2022
Accepted 15. 11. 2022
Published 1. 12. 2022

Review

OPEN ACCESS

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 **(Groh *et al.*, 2019; Żwierełło *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 **(Akhlaghi *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-tocopherols **(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 **(Żwierełło *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; Żwierełło *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 glucuronidation by UDP-glucuronyltransferase 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) **(Żwierełło *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; Żwierełło *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-glucuronide (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 with results obtained in animal experiments, demonstrating that unbound BPA exposure is reduced after oral exposure and that BPA-gluc is the predominant metabolite **(EFSA, 2015; Shih *et al.*, 2021; Teeguarden *et al.*, 2011, 2015; Thayer *et al.*, 2015; Völkel *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 **(Adegoke *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 its 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 disrupter chemical BPA as a chemical that may act as an environmental obesogen and either directly or indirectly impact fat accrual, explaining might be involvement of 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 in 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 **(Khansari *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.*, 2018; Knaze *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 inhibits BPA-induced obesity in female offspring rats and has significant modulatory action in the intestinal microbiota, implying that it could be employed in primatological 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, increased 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 research 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 BPA group in comparison with the other groups ($P\leq0.001$). Their 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 hepatocyte counts **(Bordbar *et al.*, 2021)**.

Another study investigated the effects of a methanol extract of Vincetoxicum 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 Sprague Dawley rat's blood. These data support the antioxidant 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 in the underlying mechanism of Bisphenol A-induced vascular injury. The rats were randomly separated into groups and given GSE (3 and 12 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 relaxant 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 **(Rameshrad *et al.*, 2018)**.

According to **Rameshrad *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/PI3K 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, i.p., 2 months) reversed some of BPA's negative effects on metabolic 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 **(Rameshrad *et al.*, 2019)**.

Fouad *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 **(Fouad *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 **(Fouad *et al.*, 2021)**.

Essawy *et al.* (2021) determined the therapeutic effects of astragaloside 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 nitric oxide (NO) and a reduction in glutamate (Glu), glutamine (Gln), 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 BPA+ASIV and BPA+*A. spinosus* saponins groups. Co-treatment of the BPA group with ASIV or *A. spinosus* saponin considerably reduced the values of comet parameters as well as the intensity of estrogen receptors (ERs) immunoreactive 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 **Çiğ and Yildizhan (2020)** study was to determine the mechanism by which the antioxidant resveratrol affected Transient Receptor Potential Cation Channel Subfamily M Member 2 (TRPM2)-induced oxidative stress in duct principal mpkCCDcl4 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 + RESV (in the previously mentioned concentrations). Intracellular free Ca^{2+} 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 **(Çiğ *et* Yildizhan, 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 **(Rameshrad *et al.*, 2018)**.

During a 2019 study, the antioxidant efficiency of gallic acid (GA), a polyphenol molecule derived from plants, against various toxicants 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 bisphenols, few studies have been 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 pathological context.

Acknowledgments: This work was financially supported by the Scientific Agency of the Slovak Republic VEGA No. 1/0083/21, No. 1/0038/19, No. 1/0163/18, by the Slovak Research and Development Agency Grant APVV-21-0168, APVV-21-0206, APVV-20-0218, APVV-19-0243, APVV-18-0312, and by the KEGA 023SPU-4/2022 .

REFERENCES

Adegoke, E. O., Rahman, M. S., & Pang, M.-G. (2020). Bisphenols Threaten Male Reproductive Health via Testicular Cells. Frontiers in Endocrinology, 11. http://dx.doi.org/10.3389/fendo.2020.00624

Akhlaghi, M., & Bandy, B. (2009). Mechanisms of flavonoid protection against myocardial ischemia–reperfusion injury. Journal of Molecular and Cellular Cardiology, 46(3), 309–317. http://dx.doi.org/10.1016/j.yjmcc.2008.12.003

Basu, A., Masek, E., & Ebersole, J. (2018). Dietary Polyphenols and Periodontitis—A Mini-Review of Literature. Molecules, 23(7), 1786. http://dx.doi.org/10.3390/molecules23071786

Becker, K., Güen, T., Seiwert, M., Conrad, A., Pick-Fuß, H., Müller, J., Wittassek, M., Schulz, C., & Kolossa-Gehring, M. (2009). GerES IV: Phthalate metabolites and bisphenol A in urine of German children. International Journal of Hygiene and Environmental Health, 212(6), 685–692. http://dx.doi.org/10.1016/j.ijheh.2009.08.002

Bordbar, H., Soleymani, F., Nadimi, E., Yahyavi, S. S., & Fazelian-Dehkordi, K. (2021). A Quantitative Study on the Protective Effects of Resveratrol against Bisphenol A-induced Hepatotoxicity in Rats: A Stereological Study. Iran J Med Sci., 46(3), 218–227. http://dx.doi.org/10.30476/ijms.2020.83308.1233

Bucher, S., Jalili, P., le Guillou, D., Begriche, K., Rondel, K., Martinais, S., Zalko, D., Corlu, A., Robin, M.-A., & Fromenty, B. (2017). Bisphenol a induces steatosis in HepaRG cells using a model of perinatal exposure. Environmental Toxicology, 32(3), 1024–1036. http://dx.doi.org/10.1002/tox.22301

Calafat, A. M., Ye, X., Wong, L.-Y., Reidy, J. A., & Needham, L. L. (2008). Exposure of the U.S. Population to Bisphenol A and 4- tertiary -Octylphenol: 2003–2004. Environmental Health Perspectives, 116(1), 39–44. http://dx.doi.org/10.1289/ehp.10753

Caporossi, L., & Papaleo, B. (2017). Bisphenol A and Metabolic Diseases: Challenges for Occupational Medicine. International Journal of Environmental Research and Public Health, 14(9), 959. http://dx.doi.org/10.3390/ijerph14090959

Casas, L., Fernández, M. F., Llop, S., Guxens, M., Ballester, F., Olea, N., Irurzun, M. B., Rodríguez, L. S. M., Riaño, I., Tardón, A., Vrijheid, M., Calafat, A. M., & Sunyer, J. (2011). Urinary concentrations of phthalates and phenols in a population of Spanish pregnant women and children. Environment International, 37(5), 858–866. http://dx.doi.org/10.1016/j.envint.2011.02.012

Cassidy, A., Mukamal, K. J., Liu, L., Franz, M., Eliassen, A. H., & Rimm, E. B. (2013). High Anthocyanin Intake Is Associated With a Reduced Risk of Myocardial Infarction in Young and Middle-Aged Women. Circulation, 127(2), 188–196. http://dx.doi.org/10.1161/CIRCULATIONAHA.112.122408

Churchwell, M. I., Camacho, L., Vanlandingham, M. M., Twaddle, N. C., Sepehr, E., Delclos, K. B., Fisher, J. W., & Doerge, D. R. (2014). Comparison of Life-Stage-Dependent Internal Dosimetry for Bisphenol A, Ethinyl Estradiol, a Reference Estrogen, and Endogenous Estradiol to Test an Estrogenic Mode of Action in Sprague Dawley Rats. Toxicological Sciences, 139(1), 4–20. http://dx.doi.org/10.1093/toxsci/kfu021

Çiğ, B., & Yildizhan, K. (2020). Resveratrol diminishes bisphenol A-induced oxidative stress through TRPM2 channel in the mouse kidney cortical collecting duct cells. Journal of Receptors and Signal Transduction, 40(6), 570–583. http://dx.doi.org/10.1080/10799893.2020.1769657

D'Archivio, M., Filesi, C., di Benedetto, R., Gargiulo, R., Giovannini, C., & Masella, R. (2007). Polyphenols, dietary sources and bioavailability. Annali Dell'Istituto Superiore Di Sanita, 43(4), 348–361.

Doerge, D. R., Twaddle, N. C., Vanlandingham, M., & Fisher, J. W. (2010). Pharmacokinetics of bisphenol A in neonatal and adult Sprague-Dawley rats. Toxicology and Applied Pharmacology, 247(2), 158–165. http://dx.doi.org/10.1016/j.taap.2010.06.008

Doerge, D. R., Twaddle, N. C., Vanlandingham, M., & Fisher, J. W. (2011). Pharmacokinetics of Bisphenol A in neonatal and adult CD-1 mice: Inter-species comparisons with Sprague-Dawley rats and rhesus monkeys. Toxicology Letters, 207(3), 298–305. http://dx.doi.org/10.1016/j.toxlet.2011.09.020

Dutta, M., & Paul, G. (2019). Gallic acid protects rat liver mitochondria ex vivo from bisphenol A induced oxidative stress mediated damages. Toxicology Reports, 6, 578–589. http://dx.doi.org/10.1016/j.toxrep.2019.06.011

EFSA. (2015). Report on the two-phase public consultation on the draft EFSA scientific opinion on bisphenol A (BPA). EFSA Supporting Publications, 12(1). http://dx.doi.org/10.2903/sp.efsa.2015.EN-740

Engin, A. B., & Engin, A. (2021). The effect of environmental Bisphenol A exposure on breast cancer associated with obesity. Environmental Toxicology and Pharmacology, 81, 103544. http://dx.doi.org/10.1016/j.etap.2020.103544

Essawy, A. E., Abd Elkader, H.-T. A. E., Khamiss, O. A., Eweda, S. M., & Abdou, H. M. (2021). Therapeutic effects of astragaloside IV and Astragalus spinosus saponins against bisphenol A-induced neurotoxicity and DNA damage in rats. PeerJ, 9, e11930. http://dx.doi.org/10.7717/peerj.11930

Fouad, H., Faruk, E. M., Alasmari, W. A., Nadwa, E. H., & Ebrahim, U. F. A. (2021). Structural and chemical role of mesenchymal stem cells and resveratrol in regulation of apoptotic -induced genes in Bisphenol-A induced uterine damage in adult female albino rats. Tissue and Cell, 70, 101502. http://dx.doi.org/10.1016/j.tice.2021.101502

Gao, X., Cassidy, A., Schwarzschild, M. A., Rimm, E. B., & Ascherio, A. (2012). Habitual intake of dietary flavonoids and risk of Parkinson disease. Neurology, 78(15), 1138–1145. http://dx.doi.org/10.1212/WNL.0b013e31824f7fc4

Groh, K. J., Backhaus, T., Carney-Almroth, B., Geueke, B., Inostroza, P. A., Lennquist, A., Leslie, H. A., Maffini, M., Slunge, D., Trasande, L., Warhurst, A. M., & Muncke, J. (2019). Overview of known plastic packaging-associated chemicals and their hazards. Science of The Total Environment, 651, 3253–3268. http://dx.doi.org/10.1016/j.scitotenv.2018.10.015

Janesick, A., & Blumberg, B. (2012). Obesogens, stem cells and the developmental programming of obesity. International Journal of Andrology, 35(3), 437–448. http://dx.doi.org/10.1111/j.1365-2605.2012.01247.x

Khansari N, Shakiba Y & Mahmoudi M. (2009). Chronic infammation and oxidative stress as a major cause of age-related diseases and cancer.

Knaze, V., Rothwell, J. A., Zamora-Ros, R., Moskal, A., Kyrø, C., Jakszyn, P., Skeie, G., Weiderpass, E., Santucci de Magistris, M., Agnoli, C., Westenbrink, S., Sonestedt, E., Trichopoulou, A., Vasilopoulou, E., Peppa, E., Ardanaz, E., Huerta, J. M., Boeing, H., Mancini, F. R., … Slimani, N. (2018). A new food-composition

database for 437 polyphenols in 19,899 raw and prepared foods used to estimate polyphenol intakes in adults from 10 European countries. The American Journal of Clinical Nutrition, 108(3), 517–524. http://dx.doi.org/10.1093/ajcn/nqy098
Lacagnina, S. (2020). The Developmental Origins of Health and Disease (DOHaD). American Journal of Lifestyle Medicine, 14(1), 47–50. http://dx.doi.org/10.1177/1559827619879694
Lee, I., Park, Y. J., Kim, M. J., Kim, S., Choi, S., Park, J., Cho, Y. H., Hong, S., Yoo, J., Park, H., Cheon, G. J., Choi, K., & Moon, M. K. (2021). Associations of urinary concentrations of phthalate metabolites, bisphenol A, and parabens with obesity and diabetes mellitus in a Korean adult population: Korean National Environmental Health Survey (KoNEHS) 2015–2017. Environment International, 146, 106227. http://dx.doi.org/10.1016/j.envint.2020.106227
Liao, J.-X., Chen, Y.-W., Shih, M.-K., Tain, Y.-L., Yeh, Y.-T., Chiu, M.-H., Chang, S. K. C., & Hou, C.-Y. (2021). Resveratrol Butyrate Esters Inhibit BPA-Induced Liver Damage in Male Offspring Rats by Modulating Antioxidant Capacity and Gut Microbiota. International Journal of Molecular Sciences, 22(10), 5273. http://dx.doi.org/10.3390/ijms22105273
Lorber, M., Schecter, A., Paepke, O., Shropshire, W., Christensen, K., & Birnbaum, L. (2015). Exposure assessment of adult intake of bisphenol A (BPA) with emphasis on canned food dietary exposures. Environment International, 77, 55–62. http://dx.doi.org/10.1016/j.envint.2015.01.008
Madore, M.P., Sakaki, J.R. & Chun, O.K. (2022). Protective effects of polyphenols against endocrine disrupting chemicals. Food Sci Biotechnol 31, 905–934. https://doi.org/10.1007/s10068-022-01105-z
Mhaouty-Kodja, S., Belzunces, L. P., Canivenc, M.-C., Schroeder, H., Chevrier, C., & Pasquier, E. (2018). Impairment of learning and memory performances induced by BPA: Evidences from the literature of a MoA mediated through an ED. Molecular and Cellular Endocrinology, 475, 54–73. http://dx.doi.org/10.1016/j.mce.2018.03.017
Moon, S., Yu, S. H., Lee, C. B., Park, Y. J., Yoo, H. J., & Kim, D. S. (2021). Effects of bisphenol A on cardiovascular disease: An epidemiological study using National Health and Nutrition Examination Survey 2003–2016 and meta-analysis. Science of The Total Environment, 763, 142941. http://dx.doi.org/10.1016/j.scitotenv.2020.142941
Nediani C & Giovannelli L. (2020). Oxidative stress and infammation as targets for novel preventive and therapeutic approaches in non communicable diseases. Antioxidants. 9(4): 290. http://dx.doi.org/10.3390/antiox11050824
Pandey, K. B., & Rizvi, S. I. (2009). Plant Polyphenols as Dietary Antioxidants in Human Health and Disease. Oxidative Medicine and Cellular Longevity, 2(5), 270–278. http://dx.doi.org/10.4161/oxim.2.5.9498
Rahman, M. S., Adegoke, E. O., & Pang, M.-G. (2021). Drivers of owning more BPA. Journal of Hazardous Materials, 417, 126076. http://dx.doi.org/10.1016/j.jhazmat.2021.126076
Rameshrad, M., Imenshahidi, M., Razavi, B. M., Iranshahi, M., & Hosseinzadeh, H. (2018). Bisphenol A vascular toxicity: Protective effect of Vitis vinifera (grape) seed extract and resveratrol. Phytotherapy Research, 32(12), 2396–2407. http://dx.doi.org/10.1002/ptr.6175
Rameshrad, M., Razavi, B. M., Imenshahidi, M., & Hosseinzadeh, H. (2019). Vitis vinifera (grape) seed extract and resveratrol alleviate bisphenol-A-induced metabolic syndrome: Biochemical and molecular evidences. Phytotherapy Research, 33(3), 832–844. http://dx.doi.org/10.1002/ptr.6276
Rancière, F., Botton, J., Slama, R., Lacroix, M. Z., Debrauwer, L., Charles, M. A., Roussel, R., Balkau, B., & Magliano, D. J. (2019). Exposure to Bisphenol A and Bisphenol S and Incident Type 2 Diabetes: A Case–Cohort Study in the French Cohort D.E.S.I.R. Environmental Health Perspectives, 127(10), 107013. http://dx.doi.org/10.1289/EHP5159
Reale, E., Vernez, D., & Hopf, N. B. (2021). Skin Absorption of Bisphenol A and Its Alternatives in Thermal Paper. Annals of Work Exposures and Health, 65(2), 206–218. http://dx.doi.org/10.1093/annweh/wxaa095
Recent Patents on Infammation and Allergy Drug Discovery. 3(1): 73–80. http://dx.doi.org/10.2174/187221309787158371
Rochester, J. R. (2013). Bisphenol A and human health: A review of the literature. Reproductive Toxicology, 42. http://dx.doi.org/10.1016/j.reprotox.2013.08.008
Rydén, L., Buhlin, K., Ekstrand, E., de Faire, U., Gustafsson, A., Holmer, J., Kjellström, B., Lindahl, B., Norhammar, A., Nygren, Å., Näsman, P., Rathnayake, N., Svenungsson, E., & Klinge, B. (2016). Periodontitis Increases the Risk of a First Myocardial Infarction. Circulation, 133(6), 576–583. http://dx.doi.org/10.1161/CIRCULATIONAHA.115.020324
Seachrist, D. D., Bonk, K. W., Ho, S.-M., Prins, G. S., Soto, A. M., & Keri, R. A. (2016). A review of the carcinogenic potential of bisphenol A. Reproductive Toxicology, 59, 167–182. http://dx.doi.org/10.1016/j.reprotox.2015.09.006
Shih, M.-K., Tain, Y.-L., Chen, Y.-W., Hsu, W.-H., Yeh, Y.-T., Chang, S. K. C., Liao, J.-X., & Hou, C.-Y. (2021). Resveratrol Butyrate Esters Inhibit Obesity Caused by Perinatal Exposure to Bisphenol A in Female Offspring Rats. Molecules, 26(13), 4010. http://dx.doi.org/10.3390/molecules26134010
Shu, L., Meng, Q., Diamante, G., Tsai, B., Chen, Y.-W., Mikhail, A., Luk, H., Ritz, B., Allard, P., & Yang, X. (2019). Prenatal Bisphenol A Exposure in Mice Induces Multitissue Multiomics Disruptions Linking to Cardiometabolic Disorders. Endocrinology, 160(2), 409–429. http://dx.doi.org/10.1210/en.2018-00817
Smith, C. J., Perfetti, T. A., Hayes, A. W., & Berry, S. C. (2020). Clinical epidemiology studies on potential effects of endocrine disrupting chemicals (EDCs) should exclude subjects with obesity as determined by BMI. Regulatory Toxicology and Pharmacology, 115, 104711. http://dx.doi.org/10.1016/j.yrtph.2020.104711
Tain, Y.-L., Chan, J., Lee, C.-T., & Hsu, C.-N. (2018). Maternal Melatonin Therapy Attenuates Methyl-Donor Diet-Induced Programmed Hypertension in Male Adult Rat Offspring. Nutrients, 10(10), 1407. http://dx.doi.org/10.3390/nu10101407
Tain, Y.-L., Lin, Y.-J., Chan, J. Y. H., Lee, C.-T., & Hsu, C.-N. (2017). Maternal melatonin or agomelatine therapy prevents programmed hypertension in male offspring of mother exposed to continuous light†. Biology of Reproduction, 97(4), 636–643. http://dx.doi.org/10.1093/biolre/iox115
Teeguarden, J. G., Calafat, A. M., Ye, X., Doerge, D. R., Churchwell, M. I., Gunawan, R., & Graham, M. K. (2011). Twenty-Four Hour Human Urine and Serum Profiles of Bisphenol A during High-Dietary Exposure. Toxicological Sciences, 123(1), 48–57. http://dx.doi.org/10.1093/toxsci/kfr160
Teeguarden, J. G., Twaddle, N. C., Churchwell, M. I., Yang, X., Fisher, J. W., Seryak, L. M., & Doerge, D. R. (2015). 24-hour human urine and serum profiles of bisphenol A: Evidence against sublingual absorption following ingestion in soup. Toxicology and Applied Pharmacology, 288(2), 131–142. http://dx.doi.org/10.1016/j.taap.2015.01.009
Thayer, K. A., Doerge, D. R., Hunt, D., Schurman, S. H., Twaddle, N. C., Churchwell, M. I., Garantziotis, S., Kissling, G. E., Easterling, M. R., Bucher, J. R., & Birnbaum, L. S. (2015). Pharmacokinetics of bisphenol A in humans following a single oral administration. Environment International, 83, 107–115. http://dx.doi.org/10.1016/j.envint.2015.06.008
Völkel, W., Colnot, T., Csanády, G. A., Filser, J. G., & Dekant, W. (2002). Metabolism and Kinetics of Bisphenol A in Humans at Low Doses Following Oral Administration. Chemical Research in Toxicology, 15(10), 1281–1287. http://dx.doi.org/10.1021/tx025548t
Völkel, W., Kiranoglu, M., & Fromme, H. (2008). Determination of free and total bisphenol A in human urine to assess daily uptake as a basis for a valid risk assessment. Toxicology Letters, 179(3), 155–162. http://dx.doi.org/10.1016/j.toxlet.2008.05.002
Wang, Y., Rui, M., Nie, Y., & Lu, G. (2018). Influence of gastrointestinal tract on metabolism of bisphenol A as determined by in vitro simulated system. Journal of Hazardous Materials, 355, 111–118. http://dx.doi.org/10.1016/j.jhazmat.2018.05.011
Wedick, N. M., Pan, A., Cassidy, A., Rimm, E. B., Sampson, L., Rosner, B., Willett, W., Hu, F. B., Sun, Q., & van Dam, R. M. (2012). Dietary flavonoid intakes and risk of type 2 diabetes in US men and women. The American Journal of Clinical Nutrition, 95(4), 925–933. http://dx.doi.org/10.3945/ajcn.111.028894
Zahra, Z., Khan, M. R., Majid, M., Maryam, S., & Sajid, M. (2020). Gonadoprotective ability of Vincetoxicum arnottianum extract against bisphenol A-induced testicular toxicity and hormonal imbalance in male Sprague Dawley rats. Andrologia, 52(6). http://dx.doi.org/10.1111/and.13590
Zhao, H., Zhu, W., Jia, L., Sun, X., Chen, G., Zhao, X., Li, X., Meng, X., Kong, L., Xing, L., & Yu, J. (2016). Phase I study of topical epigallocatechin-3-gallate (EGCG) in patients with breast cancer receiving adjuvant radiotherapy. The British Journal of Radiology, 89(1058), 20150665. http://dx.doi.org/10.1259/bjr.20150665
Żwierełło, W., Maruszewska, A., Skórka-Majewicz, M., Goschorska, M., Baranowska-Bosiacka, I., Dec, K., Styburski, D., Nowakowska, A., & Gutowska, I. (2020). The influence of polyphenols on metabolic disorders caused by compounds released from plastics - Review. Chemosphere, 240, 124901. http://dx.doi.org/10.1016/j.chemosphere.2019.124901