J. Fac. Pharm. Ankara / Ankara Ecz. Fak. Derg., 48(2): 552-558, 2024
Doi: 10.33483/jfpau.1428739

ORIGINAL ARTICLE / ÖZGÜN MAKALE

DETERMINATION OF DNA DAMAGE INDUCED BY BISPHENOL A AND BISPHENOL S IN MCF7 CELL LINE

BİSFENOL A VE BİSFENOL S'NİN MCF7 HÜCRE HATTINDA NEDEN OLDUĞU DNA HASARININ ARAŞTIRILMASI

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ABSTRACT

Objective: *This study aimed to determine the DNA damage induced by Bisphenol A (BPA) and Bisphenol S (BPS) on MCF7 cell line.*
Material and Method: *DNA damage was determined by COMET assay in MCF7 cell line at 0.1, 0.5, 1, 5, 10 and 50 µM concentrations of BPA and BPS.*
Result and Discussion: *All BPA and BPS concentrations studied (0.1, 0.5, 1, 5, 10 and 50 µM) significantly induced DNA damage on MCF7 cell line compared with control ($p<0.05$). BPS significantly induced DNA damage more than BPA at the 3 highest concentrations studied (5, 10 and 50 µM) ($p<0.05$). This study shows that bisphenol derivatives can also cause DNA damage like BPA.*
Keywords: *Bisphenol A, bisphenol S, COMET assay, DNA damage, MCF7 cell line*

ÖZ

Amaç: *Bu çalışmada, Bisfenol A (BPA) ve Bisfenol S (BPS)'nin MCF7 hücre hattında neden olduğu DNA hasarının belirlenmesi amaçlanmıştır.*
Gereç ve Yöntem: *DNA hasarı BPA ve BPS'nin 0.1, 0.5, 1, 5, 10 ve 50 µM konsantrasyonlarda MCF7 hücre hattında COMET yöntemi ile belirlenmiştir.*
Sonuç ve Tartışma: *Çalışılan tüm BPA ve BPS konsantrasyonları (0.1, 0.5, 1, 5, 10 ve 50 µM) MCF7 hücre hattında kontrole kıyasla önemli ölçüde DNA hasarına neden olmuştur ($p<0.05$). BPS, çalışılan en yüksek 3 konsantrasyonda (5, 10 ve 50 µM) DNA hasarını BPA'dan daha fazla indüklemiştir ($p<0.05$). Bu çalışma bisfenol türevlerinin de BPA gibi DNA hasarına neden olabileceğini göstermektedir.*
Anahtar Kelimeler: *Bisfenol A, bisfenol S, COMET testi, DNA hasarı, MCF7 hücre hattı*

INTRODUCTION

Bisphenol A (BPA) is among the most produced chemicals worldwide. BPA was first synthesized by Dianin in 1891 and was extensively researched in the 1930s during studies to produce synthetic

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Submitted / Gönderilme : 13.02.2024
Accepted / Kabul : 14.03.2024
Published / Yayınlanma : 20.05.2024

estrogen. After this date, it was suggested that BPA could be used to make plastics, and in the 1940s it began to be used in resin production. The polymerization of BPA by Bayer and General Electric was discovered in 1957, leading to the use of polycarbonate for beverage and food packaging. This development led to a rapid increase in the use of BPA in plastic making, making it the most widely used commercial product in the world [1,2]. As a result, the widely used BPA monomers, polycarbonate (PC), were found to be released from plastics into the ecosystem and food [3,4]. Various reports indicate that BPA in plastic food containers, paper money, personal care products, and toys may cause reproductive, developmental, and carcinogenic effects. Many *in vivo* and *in vitro* studies demonstrated that BPA negatively affects human health with its endocrine-disrupting effects [5-7].

BPA acts as an endocrine disruptor that alters the histological structure of cells and causes biochemical and physiological changes that modify the functions of tissues and organs. When it is looked at its effects in the reproductive system, it is seen it shows a weak estrogenic effect by binding to estrogen receptors and that the main target is ovarian granulosa cells. Disruption of these cells by BPA plays an important role in fertility. As MCF7 is estrogen-positive, it is considered one of the most suitable cell lines to study bisphenols that mainly affect the reproductive system. In addition, it interacts with androgen receptors, peroxisome proliferator active receptors, and other endocrine system receptors [8,9]. BPA can bind to androgen receptors by acting like androgen and can cause specific changes in gene expression. Considering its effect on the androgen receptor, BPA is a known antagonist. It slows down nuclear transport and forms non-functional foci in the nucleus [10,11].

According to the report that FDA (Food and Drug Administration) released in 2010, fetuses, infants, and children may develop brain, behavioral, and prostate abnormalities if they are exposed to BPA in their early years. Several states have banned the use of BPA since then. In 2011, the European Union (EU) banned BPA-containing baby bottles and in 2013, a maximum allowable dose level (MADL) of 290 micrograms per day has been established for BPA exposure by the Office of Environmental Health Hazard Assessment (OEHHA) [12,13].

The demonstration of the toxicity of BPA in numerous studies has encouraged the industry to search for alternative chemicals. As a result, manufacturers started to remove this compound from their BPA-containing products and gradually transitioned to the use of bisphenol analogs, such as Bisphenol S (BPS), Bisphenol AF (BPAF), Bisphenol Z (BPZ), and Bisphenol F (BPF). However, these analogs are still bisphenols and have the potential to have toxic effects similar to BPA. Toxicological information on the endocrine-disrupting potential of these compounds is limited and little is known about their toxicity. Particularly in recent years, the use of the least toxic bisphenol compound in food contact products has been emphasized [14,15].

Among these analogs, the use of BPS has become increasingly common in recent years due to its resistance to high temperatures and sunlight and its lower toxicity. BPS is widely used in many industrial areas for cleaning purposes, in "BPA-free" thermal papers, as a primer, especially in pipes to increase thickness and durability, in industrial floors, on the tops of roads and bridges, and in epoxy resin construction and coatings. BPS is found in many personal care products used in daily life such as body gels, hair care products, make-up, lotions, and toothpaste, paper products such as money, tickets, flyers, airplane boarding cards, dairy products, vegetables, boxed foods, and human exposure to bisphenols continues [15,16].

Although products such as water bottles, baby bottles, toys, and personal care products have remarkable labels such as "BPA free", these products contain bisphenols. In addition, the toxicity profiles of these newly introduced bisphenol analogs have not been fully elucidated. There are many studies on BPA, but detailed toxicological investigations of other bisphenol analogs should be carried out and shown if they have similar toxic effects as BPA and should be regulated to the limit values of use by legal authorities. It is important to raise public awareness and inform the producers and consumers about this issue. For this purpose, in this study, DNA damage caused by BPA and BPS on MCF7, a breast cancer cell line, was studied by COMET assay.

MATERIAL AND METHOD

Chemicals

Hydrogen peroxide (H_2O_2), phosphate-buffered saline (PBS), bisphenol A (BPA), bisphenol S (BPS), and low melting point agarose (LMPA) were obtained from Sigma-Aldrich (Germany). Fetal bovine serum (FBS) was bought from Biological Industries (Israel). Dulbecco's Modified Eagle's Medium (DMEM) and trypsin were products of Sartorius (Israel). Dimethyl sulfoxide (DMSO) was bought from Serva (USA). Sodium hydroxide (NaOH) and triton-X 100 were purchased from Merck (Germany). Penicillin/Streptomycin (Pen/Strep) was obtained from Gibco (USA) and sodium chloride (NaCl) was from Zag Kimya (Türkiye). Disodium ethylenediaminetetraacetic acid (Na_2EDTA) and tris were purchased from VWR Chemicals (USA). Normal melting point agarose (NMPA), ethidium bromide and sodium sarcosinate were bought from Amresco (USA).

COMET Assay

As a preliminary study, cytotoxicity assays of BPA and BPS at concentrations of 0.1, 0.5, 1, 5, 10, 50, 100, and 500 µM were performed in order to assess cell viability in MCF7 (ATCC® HTB-22™) cell line for 24 h [17].

The standard method [18] was the foundation for the alkaline COMET assay, with a few minor adjustments. COMET assay was performed in 6-well plates at 2 x 104 /2 ml cells/well. BPA and BPS solutions were prepared with sterile DMSO. Based on the preliminary study, concentrations below the IC_{50} values of 0.1, 0.5, 1, 5, 10, and 50 µM BPA and BPS were applied to wells. H_2O_2 at 50 µM served as the positive control. Since DMSO was used as a solvent for bisphenol compounds, a control containing 0.1% DMSO was used100 µl of melted LMPA (0.5%) was combined with 50 µl of cell suspension (1-2 x 104 cells/slide) at 37˚C. After spreading cell suspensions with 1% NMPA on the pre-coated slides, a coverslip was placed over them. The agar was left to firm for about five minutes on a flat, ice-cold tray. A cold lysing solution (10 mM Tris, 2.5 M NaCl, 100 mM Na_2EDTA, 1% sodium sarcosinate, 1% Triton-X 100, 10% DMSO, pH 10.0) was prepared ahead of time, and the slides were submerged in it for at least an hour at 4˚C. An adequate amount of cold electrophoresis solution (1 mM Na_2EDTA, 300 mM NaOH, pH=13) was added to the electrophoresis tank. The slides that had been taken out of the lysing solution were put in the electrophoresis tank, where they were electrophoresed for 20 minutes at 25 V and 300 mA after being left in this solution for 20 minutes to allow for denaturation. The electrophoresed slides were removed from the electrophoresis tank and then rinsed three times for five minutes each in a neutralizing solution (0.4 M Tris, pH 7.5). The cells were fixed on the slides with alcohol and stored in a humid condition until analysis. Following 10 minutes of staining with 60 µl (20 µg/ml) ethidium bromide solution, slides were analyzed under a microscope. A Leica DM 1000 fluorescent microscope was used to examine 100 randomly chosen cells per slide at 40x magnification., and the COMET Assay IV software (Perceptive Instruments, UK) was used to count the cells. One researcher scored the DNA damage, and the damage was reported as a mean tail intensity percentage. COMET assays were performed in duplicate at different times.

Statistical Analysis

The SPSS software (SPSS Windows Release 23.0, SPSS Inc., USA) was used to conduct statistical analyses. The findings were presented as mean ± standard error of mean (SEM). DNA Tail Intensity values of all 100 cell counts for each sample were used as control and test chemicals groups in the evaluation of COMET assay results and were evaluated by one-way analysis of variance (ANOVA). Fischer's least significant difference test (LSD) was utilized for post-hoc analysis (comparison among groups). p-value lower than 0.05 ($p<0.05$) was regarded as statistically significant.

RESULT AND DISCUSSION

In the preliminary study, BPA and BPS concentrations that reduce cell viability by 50% (IC_{50}) for MCF7 cell line were calculated as 45 µM and 450 µM, respectively [17].

To assess genotoxicity, one researcher randomly selected 100 cells per sample and scored them using COMET Assay IV Software. The mean % tail intensity values of BPS and BPA were used to evaluate the COMET assay (Figure 1).

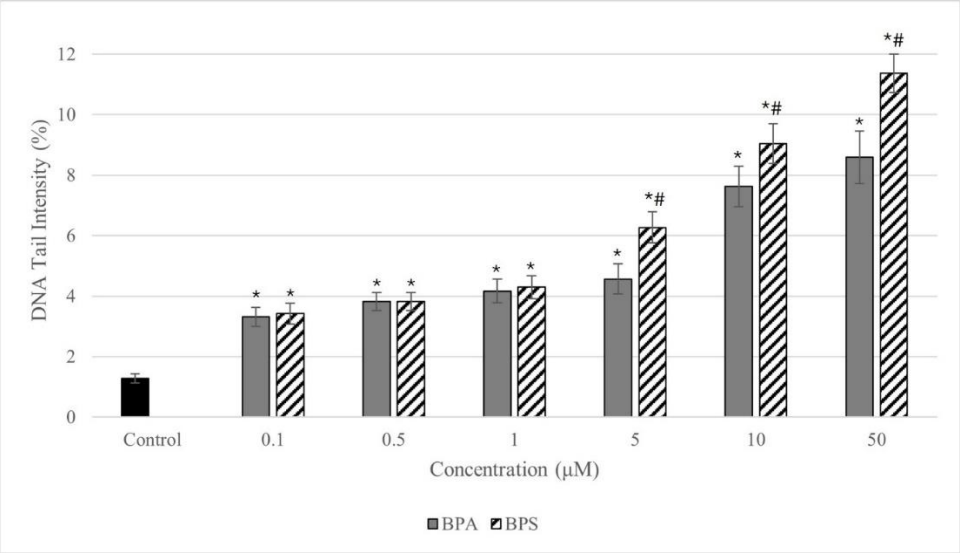

Figure 1. DNA damage in MCF7 versus increasing concentrations of BPA and BPS. The mean tail intensity of the groups was compared using a one-way ANOVA (n=100) (control: solvent (0.1%DMSO), BPA: Bisphenol A, BPS: Bisphenol S. *p<0.05: statistically significant vs control # p<0.05: statistically significant vs BPA at the same concentrations

Mean tail intensity results of cells that were exposed to BPA and BPS at increasing doses are shown in Table 1. When compared to the control, all studied doses of BPA, BPS, and 50 µM H_2O_2 significantly caused DNA damage in MCF7 (p<0.05). BPS significantly induced DNA damage more than BPA at the 3 highest concentrations studied (5, 10, and 50 µM).

Table 1. % DNA Tail Intensity results of chemicals on MCF7 cell line

Chemicals	Concentrations (µM)	% DNA Tail Intensity ± SEM
Control		1.28±0.1513
BPA	0.1	3.31±0.3132*
	0.5	3.82±0.3006*
	1	4.17±0.3898*
	5	4.57±0.4982*
	10	7.62±0.6732*
	50	8.59±0.8653*
BPS	0.1	3.42±0.3438*
	0.5	3.82±0.3005*
	1	4.30±0.3750*
	5	6.27±0.5177*#
	10	9.04±0.6559*#
	50	11.37±0.6394*#
H_2O_2		25.2166±9.4795*

*Concentrations that significantly induced DNA damage in MCF7 compared with control (p<0.05)
#Concentrations that significantly induced more DNA damage in MCF7 compared with BPA at the same concentrations (p<0.05)

In a study by He et al. investigating the role of brain-derived neurotrophic factor signaling pathway in BPS-induced cytotoxicity in human neuroblastoma cell line (SK-N-SH), cells were exposed to BPS at concentrations of 100, 200, and 300 µmol/L and cell viability was examined. It was observed that cell viability decreased in a dose-dependent manner and cell morphology was changed. As a result of 24 hours of BPS exposure in this cell line, IC_{50} value was calculated as 285.84 µmol/L. It was also observed that the apoptosis rate increased in cells in a dose-dependent manner [19]. Feng et al. investigated the potential endocrine-disrupting effects of bisphenol A and its derivatives on human adrenocortical carcinoma cell line (H295R) and exposed cells to BPA, BPS, BPF, and BPAF at increasing doses of 10-500 µM for 24 hours, 48 hours and 72 hours. The viability of cells was measured using the Cell Counting Kit-8 (CCK-8) and it was observed that cytotoxicity increased as exposure time and concentrations increased. After 72 hours of exposure, the LC_{50} (Lethal Concentration 50) value was calculated as 103.4 µM for BPA and 159.6 µM for BPS and it was reported that BPA was more cytotoxic than BPS [20]. These findings support our study which we also found that BPA was more cytotoxic than BPS. In a study investigating the levels of cytotoxicity, reactive oxygen species (ROS), and DNA damage due to BPA and BPS exposure in human bronchial epithelial cells (BEAS-2B), cells were exposed to BPA and BPS at concentrations of 12.5, 25, 50, 100 and 200 µM. To measure cell viability, MTS assay was performed after 24 hours of exposure and IC_{50} values were calculated above 200 µM for both bisphenol derivatives. In the COMET assay to examine DNA damage, tail intensities were measured, and it was found that BPA induced DNA damage more than BPS. They stated that this may be due to increased ROS production [21]. In another research, human peripheral blood mononuclear cells (PBMCs) were exposed to BPA, BPF, BPAF, and BPS, and alkaline and neutral COMET assays were performed as a result of 1-hour and 4-hour exposures. In the alkaline COMET assay, BPA induced DNA damage at concentrations of 0.1, 1, and 10 µg/ml after 1 h exposure and at concentrations of 0.01, 0.1, 1, and 10 µg/ml after 4 h exposure; whereas BPS induced DNA damage only at a concentration of 10 µg/ml after 4 h exposure. It was discovered that BPA damaged DNA in the neutral COMET assay at concentrations of 1 and 10 µg/ml following a 1-h exposure.; however, BPA and BPS only caused DNA damage at a dose of 10 µg/ml after 4-h exposure. As a result of these studies, it was stated that the genotoxic potential of BPA was higher than that of BPS [22]. However, in our study we found that BPS was more genotoxic than BPA, especially at 5, 10 and 50 µM. BPA, BPS and other bisphenol derivatives were used in a study investigating the mutagenicity and DNA damage of bisphenol derivatives on HepG2 cell line. Using Salmonella typhimurium strains TA98 and TA 100, the AMES test was used to examine the mutagenicity of bisphenol derivatives. At dosages of 0.004, 0.02, 0.1, and 0.5 mg, the test revealed no mutagenic activity. When using MTT as a test for cell viability at 24 hours of exposure, there wasn't any decrease in viability at concentrations of 12.5, 25, 50, and 100 µmol/L. Genotoxicity potentials were studied at concentrations of 0.1, 1, and 10 µmol/L by COMET assay, and DNA strand breaks were observed at all studied concentrations of BPA and 0.1 and 10 µmol/L concentrations of BPS in 24 h exposure [23]. In the study by Kose et al. on the toxicity of BPA, BPF, and BPS on prostate cell line (RWPE-1), cell viability was determined by MTT test, and IC_{50} values were calculated as 113.74, 249, and 380.90 µM, respectively. IC_{20} values for BPA, BPF, and BPS were calculated as 45, 65, and 108 µM, respectively, and these concentrations were used in the alkali COMET assay. Genotoxic potentials were observed as BPS > BPF > BPA [24]. These results support our findings that even though BPA is more cytotoxic than BPS, when DNA damage is investigated, BPS seems to be more genotoxic than BPA. In a study examining whether BPS causes epigenetic changes in MCF7 cell line, cells were exposed to 1 mM, 100 nM and 10 nM BPS for 24 hours. At the end of the experiment, it was observed that BPS induced DNA methylation [25]. However, it is seen that there were no studies examining the direct DNA damage caused by BPS on MCF7 cell line.

In conclusion, the chemical compound BPA is widely produced and used in plastics. After its use in food and beverage packages, BPA's widespread use increased, and it was later found to have endocrine-disrupting properties. After the increase in research on BPA and the confirmation of its toxic effects, the use of BPA was restricted and banned in most countries around the world. After these bans, the industry started to search for derivatives that could replace BPA. With the introduction of BPA derivatives into industrial use, it has been a matter of debate whether BPS, one of the most widely used derivatives, shows toxic effects like BPA. Our study aims to shed light on this issue. Our study showed

that although BPA was more cytotoxic than BPS, at high concentrations BPS was more genotoxic than BPA. Further studies on the toxicity of bisphenol derivatives are needed to determine whether they are safe to use.

ACKNOWLEDGEMENTS

Ekin Erdogmus's doctoral thesis from the Health Sciences Institute at Ankara University served as the basis for this work. With a grant number of TDK-2022-2702, the Ankara University Scientific Research Projects Coordination Unit provided funding, which the authors gratefully recognize.

AUTHOR CONTRIBUTIONS

Concept: B.K.G., Y.D., A.U.; Design: A.U.; Control: B.K.G., Y.D., A.U.; Sources: E.E., A.U.; Materials: Y.D., A.U.; Data Collection and/or Processing: E.E., A.U.; Analysis and/or Interpretation: E.E., S.I.T.; Literature Review: E.E., S.I.T., A.U.; Manuscript Writing: E.E., A.U.; Critical Review: E.E., S.I.T., B.K.G., Y.D., A.U.; Other: E.E., S.I.T., B.K.G., Y.D., A.U.

CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that ethics committee approval is not required for this study.

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