Turkish Journal of Agriculture - Food Science and Technology, 12(10): 1746-1752, 2024
DOI: https://doi.org/10.24925/turjaf.v12i10.1746-1752.7122

Turkish Journal of Agriculture - Food Science and Technology

Available online, ISSN: 2148-127X | www.agrifoodscience.com | Turkish Science and Technology Publishing (TURSTEP)

Neuroprotective Efficacy of β-caryophyllene on Cerebellar Changes Caused by Bisphenol A in Rats via Alleviating Oxidative Stress

Ahmad Yahyazadeh[1,a,*], Fatih Mehmet Gür[2,b], Hatice Yaren Kuloğlu[3,c]

[1]*Department of Histology and Embryology, Faculty of Medicine, Karabuk University, Karabuk, Türkiye*
[2]*Department of Histology and Embryology, Faculty of Medicine, Nigde Omer Halisdemir University, Niğde, Türkiye*
[3]*Department of Histoloy and Embriology, Faculty of Veterinary Medicine, Aksaray University, Aksaray, Türkiye*
[*]*Corresponding author*

ARTICLE INFO

Research Article

Received : 11.09.2024
Accepted : 30.09.2024

Keywords:
β-caryophyllene
Bisphenol A
Cerebellum
Male rat
Stereology

ABSTRACT

Exposure to bisphenol A (BP), an environmental pollutant, is potentially harmful to both human health and the environment. The purpose of the current research was to evaluate the effectiveness of β-caryophyllene (CF) (200 mg/kg) on rat cerebellar tissues exposed to BP (250 mg/kg). Thirty-five randomly selected male rats were split into five groups as: control (CON), olive oil (OL), BP, CF, and CF+BP. On day 15 of the experiment, all rats' cerebellar tissues were immediately extracted, followed by stereological and histological examination. Our results revealed that MDA level was significantly elevated in the BP group compared to the CON group ($p<0.05$). While no significant difference was detected in the mean cerebellar volume among the experimental groups, the BP group's the Purkinje cell number was significantly reduced when compared to the CON group ($p<0.05$). In the CF+BP group, we found a significantly lower level of MDA and higher number of Purkinje cells compared to the BP group ($p<0.05$). Histopathological examination revealed that the BP group had the marked neuronal deterioration; however, in the CF+BP group, this structural alteration was not as severe than the BP group. Our findings showed that exposure to BP caused oxidative damage to cerebellar tissues, and administration of CF attenuated BP-induced toxicity via improvement of oxidative stress.

[a] *yahyazadeh.ahmad@karabuk.edu.tr* *https://orcid.org/0000-0002-6093-3588*
[b] *fgur@ohu.edu.tr* *https://orcid.org/0000-0001-7748-3272*
[c] *haticeyyaren@gmail.com* *https://orcid.org/0000-0003-0435-4677*

Introduction

Bisphenol A (BP) is one of the most widely produced chemicals worldwide, which is frequently found in the environment. Following their entry into the body via different routes, BP is accumulated in a variety of vital tissues (Vandenberg et al., 2007). Due to its extensive use, this hazardous chemical pollutant poses a risk to public health due to a serious adverse effect on the biosystem (Yahyazadeh, 2024b). Experimental studies have revealed that toxicity of BP may be associated with disorder in the nervous, reproductive, cardiovascular, metabolic, and immune systems (Cooper & Posnack, 2022; Costa & Cairrao, 2024). It acts as an agonist or antagonist through endocrine receptor-dependent signalling pathways (Maniradhan & Calivarathan, 2023). Therefore, the cause of numerous endocrine problems may be related to BPA. Previous scientific research has indicated a connection between BP treatment and obesity prevalence, impaired glucose tolerance, and abnormal lipid metabolism in mice (Newbold et al., 2009). Exposure to BS has also been reported to interfere with the structure and functioning of the nervous system (CNS) (Khan et al., 2019). As suggested by experimental studies, exposure to BP contributes to disruption of the neuroendocrine system (Ma et al., 2019).

The central nerve system (CNS) is among the body's most susceptible systems to oxidative stress, which may sustain further damage (Suresh & Vellapandian, 2024). BP has been reported to be associated with oxidative damage to multiple organ tissues. As an indicator of oxidative stress, malondialdehyde (MDA) is an important product formed by the peroxidation of fatty acids containing multiple bonds (Amini et al., 2023). An earlier study suggested that MDA level was significantly elevated in the nervous system following exposure to BP (Abdou et al., 2022).

A crucial group of compounds, antioxidants, is thought to be beneficial to help inhibit or reduce free radical-induced damage to vital tissues. β-caryophyllene (CF), a phytocannabinoid, renowned for its safety and beneficial nutrients, is commonly found in high concentrations in spices.

The therapeutic potential of CF has been attributed to its anticancer, anti-inflammatory, anti-apoptotic, and antioxidant properties (Al-Taee et al., 2019; Mannino et al., 2021).

The current experimental investigation was aimed to gain insight into the potential hazards of BP on cerebellar tissues in Wistar albino rats. We also surveyed the antioxidant capability of CF on BP-induced alteration in the cerebellum tissues using stereological, biochemical, histopathological techniques.

Materials and Methods

In this research, 35 male Wistar albino rats (8-10 weeks of age and body weight of 180-200 g) were employed. The Karabuk University Laboratory Animal Ethics Committee granted this study ethical approval (Protocol No. 2023/10/28). Rats were kept in a plastic cage with 12 hours of darkness and light, a temperature of 21–24 ºC, and 45–55% humidity. Each subject had unrestricted access to tap water and a standard chow diet throughout the trial. After being randomly split up into five groups (n = 7), rats underwent the following experimental procedures:

- *Control (CON) group:* Animals received no substance during for 14 days.
- *Olive oil (OL) group:* Animals were administrated OL orally for a period of 14 days.
- *Bisphenol A (BP) group:* Animals were administered 250 mg/kg BP orally for 14 days (Vanani et al., 2020).
- *β-caryophyllene (CF) group:* Animals received 200 mg/kg CF orally for 14 days (Refaat & El-Boshy, 2022).
- *β-caryophyllene + bisphenol A (CF+BP) group:* Animals were administered 200 mg/kg CF orally for 14 days. Moreover, 250 mg/kg BP was given via oral rout to each rat for 14 days.

Upon completion of the trial, animals received intraperitoneal injections of xylazine (6–8 mg/kg) and ketamine (60–80 mg/kg) to induce anaesthesia. First, blood samples were collected through intracardial puncture, then placed in heparinized tubes. After sacrificing subject, their cerebella were harvested for the histopathological evaluation and stereological examination. Furthermore, serum was collected from blood collection tubes centrifuged for 10 minutes at 3500 rpm. All serum samples were then stored at -80°C for biochemical analysis.

Histological Study

The cerebellar tissues were fixed using a 10% neutral formalin fixative for 48 h. The histological tissues were then processed by running them through a series of graded alcohols, xylene, and paraffin. After embedding in paraffin as an ideal medium, cerebellar tissue blocks were sectioned into 7 µm-thickness using a rotary microtome. All sections were then placed on glass slides, followed by an overnight incubation at 60°C in an oven to remove excess paraffin. Finally, sections stained with cresyl violet were studied using a Leica HD digital camera-equipped LED microscope (Leica DM2500).

Biochemical Analysis

Measurement of MDA level was carried out in accordance with the technique of an earlier study (Yoshioka et al., 1979), which was based on reaction with thiobarbituric acid (TBA) at 90–100°C. MDA concentration was also given as nmol/ml.

Stereological Study

To determine the mean volumes of the cerebellum and its main components, we adapted the point-counting grid and Cavalieri techniques (Yahyazadeh, 2024a). Each section's region of interest was first photographed, then microscopic photographs were randomly overlaid with a point-counting grid. After it was determined the number of points that had hit the region of interest, the points were counted. Ultimately, areas (A) of cerebella and their parts were calculated as:

$$\mathrm{Area(A)} = \mathrm{a(p)} \times \sum \mathrm{P}$$

Where the number of counted points is represented by "ΣP", and the area of the point interval is denoted by "a(p)". The mean volumes (V) of the cerebella and their parts were then calculated as follows:

$$\Sigma \mathrm{V} = \Sigma \mathrm{A} \times \mathrm{t}$$

where the total thickness of sections and intervals is represented by "t", and the area of the regions of interest in cerebella is denoted by "ΣA".

Physical disector was also employed as a comparative tool in the stereology to provide an unbiased estimation of the neuron number. The pairs are made up of the consecutive sections, which consist of the reference sections and look-up at a specific distance. The counting frame was placed on the disector pairs following the localization of the corresponding fields. Nerve cells were then counted in the pairs' identical fields. Prior to estimating the Purkinje neuron number, their numerical density (Nv) was first computed using the following formula:

$$\mathrm{Nv} = \frac{\sum \mathrm{Q} -}{\sum \mathrm{V\ disector}}$$

where "ΣV disector" refers to the total disector frame volumes, and "ΣQ" refers to the counted neuron number in the pairs. The Purkinje cell number (N) was ultimately estimated as:

$$\mathrm{N\ (number\ of\ neurons)} = \mathrm{N_V} \times \mathrm{V_{ref}}$$

where "Nv" refers to the numerical density of Purkinje cells, and "Vref" refers to the mean volume of cerebellar tissues.

Statistical Analysis

IBM SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA) was employed for analysing the quantitative data of stereology and biochemistry. Given that the data were regularly distributed, the parametric analysis was chosen. The Tukey's post hoc test and the One-Way ANOVA have been employed to compare the differences between groups. We expressed the data as the mean ± standard deviation. Besides, p value less than 0.05 was the threshold adopted to define statistical significance for the results.

Results and discussion

Biochemical results

The biochemical data of MDA level are given in Figure 1. Our finding indicated that the MDA level, a marker for oxidative stress, was significantly higher in the BP group when compared to the CON ($p<0.05$), OL ($p<0.05$), and CF ($p<0.01$) groups. In the CF+BP group, significantly lower level of MDA was detected Compared to the BP group ($p<0.05$).

Stereological Results

The Purkinje cell number is given in Figure 2. The Purkinje cells number in the BP group was significantly lower when compared to the CON ($p < 0.01$), OL ($p < 0.01$), and CF ($p < 0.01$) groups. In the CF+BP group, it was determined to be significantly higher compared to the BP group ($p < 0.05$). Furthermore, a significant reduction of Purkinje cell number was detected in the CF+BP group when compared to the CON ($p < 0.01$) and CF ($p < 0.01$) groups.

The mean volumes of grey matter are given in Figure 3. Given the statistical analysis of data, the mean grey matter volume was not significantly different between the BP and CON groups or the CF+BP and BP groups. A significant elevation was observed in the BP group compared to the CF group ($p < 0.05$).

The mean volumes of white matter are given in Figure 4. Our data showed no significant difference between the BP group and the CON group. Besides, the mean white matter volume was significantly higher in the BP group when compared to the CF group ($p < 0.05$).

The mean volumes of cerebella are given in Figure 5. The BP group's mean cerebellar volume was significantly higher compared to the CF group ($p < 0.05$), but there was no significant difference among other groups.

The volume fraction ratios of grey matter to cerebellum are given in Figure 6. Our finding revealed no statistically significant difference in the volume ratio of grey matter to cerebellum among all groups

The volume fraction ratios of white matter to cerebellum are given in Figure 7. No significant difference was found in the volume ratio of white matter to cerebellum among all groups.

The volume fraction ratios of grey matter to white matter are given in Figure 8. Statistical analysis of data indicated no significant difference in the volume fraction ratio of grey matter to white matter among all groups.

Histopathological Results

The histopathological examination of cerebellar tissues exhibited healthy and intact structures in the CON, OL, and CF groups (Figure 9). In contrast, there was marked alteration in cerebellar tissue's architectures in the BP group (Figure 10a and b). Our finding revealed degeneration in Purkinje cells and vascular congestion in cerebellar tissues. Although structural alterations were observed in the CF+BP group, they were less pronounced than the BP group (Figure 10 c and d).

Given our biochemical finding, the exposure to BP contributed to significantly higher levels of MDA in the BP group than the CON group. A possible reason for this change was due to an oxidative imbalance induced by an increased generation of ROS after exposure to BP.

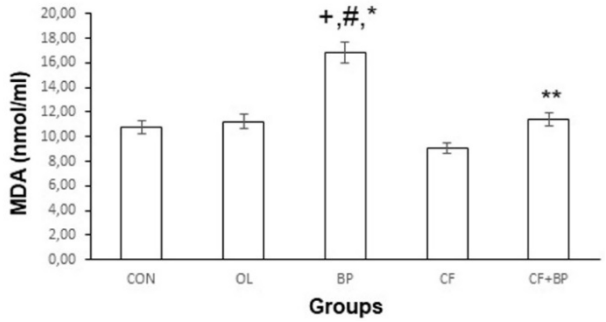

Figure 1. MDA levels. +, significantly different from the CON group; #, significantly different from the OL group; asterisk, significantly different from the CF group; double asterisk, significantly different from the BP group

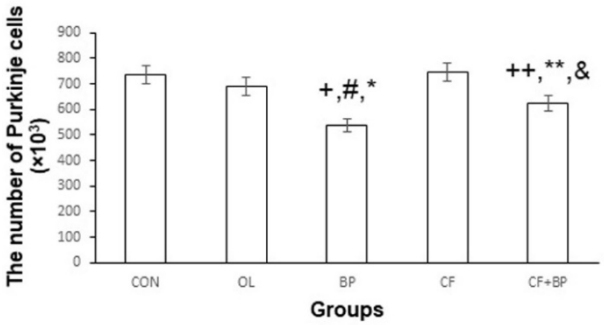

Figure 2. The Purkinje cells number. +, significantly different from the CON group; #, significantly different from the OL group; asterisk, significantly different from the CF group; ++, significantly different from the CON group; double asterisk, significantly different from the BP group; &, significantly different from the CF group

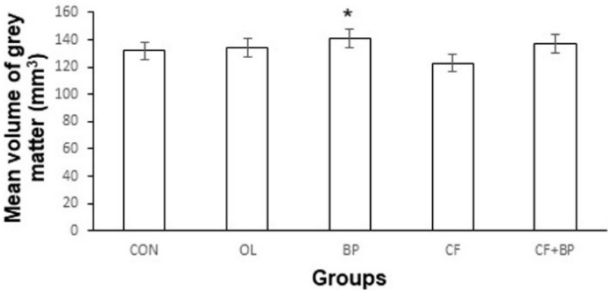

Figure 3. The mean volume of cerebellar grey matter. Asterisk, significantly different from the CF group

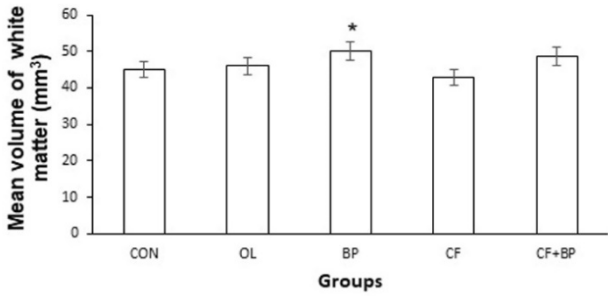

Figure 4. The mean volume of cerebellar white matter. Asterisk, significantly different from the CF group

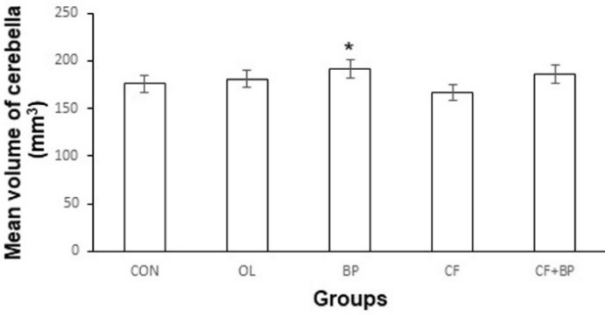

Figure 5. The mean volumes of cerebella. Asterisk, significantly different from the CF group

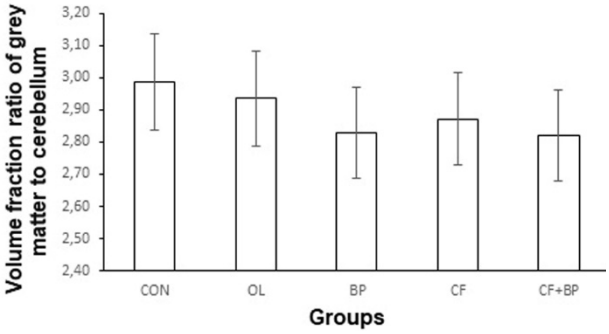

Figure 6. The volume fraction ratio of grey matter to cerebellum

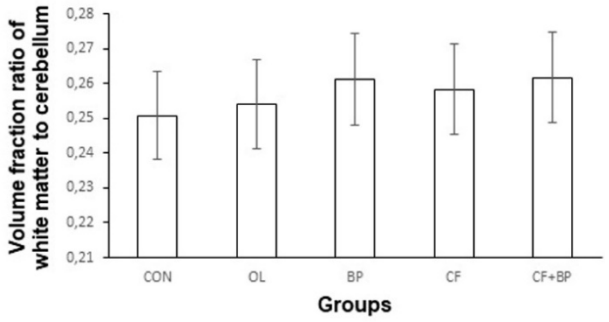

Figure 7. The volume fraction ratio of white matter to cerebellum

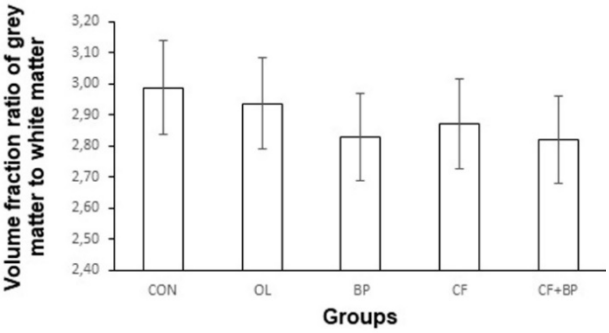

Figure 8. The volume fraction ratio of grey matter to white matter

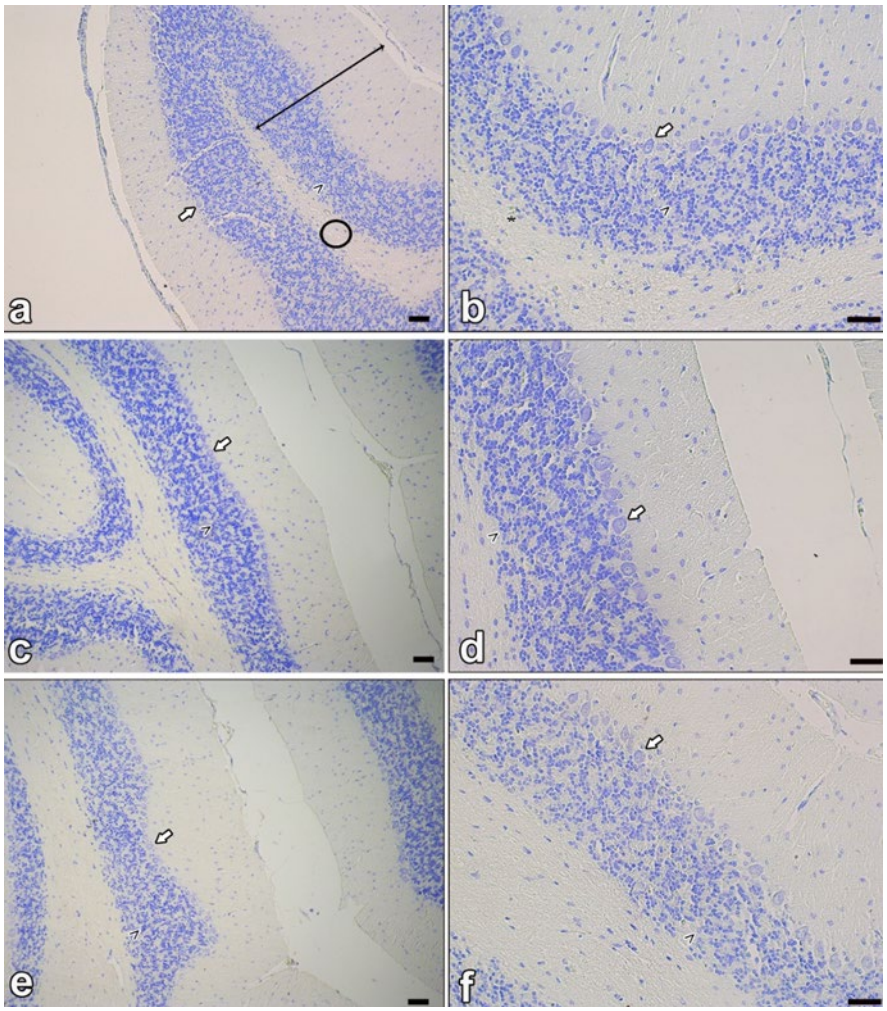

Figure 9. Micrographs of cerebellar tissues in the CON (a and b), OL (c and d), and CF (e and f) groups. White arrow, intact Purkinje cells; asterisk, blood vessel; circle, white matter; double-headed arrow, grey matter; arrowhead. Scale bars = 25 µm

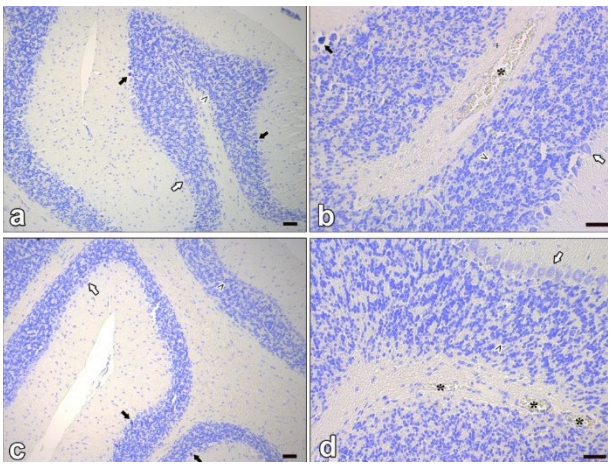

Figure 10. Micrographs of cerebellar tissues in the BP (a and b) and CF+BP (c and d) groups. White arrow, intact Purkinje cells; black arrow, degenerated Purkinje cells; asterisks, vascular congestion arrowhead, granular cells. Scale bars = 25 µm

In alignment with our research, the CNS neurotoxicity caused by oxidative stress has been shown to be linked to BP exposure (Khan et al., 2019). MDA formation can cause major damage to membrane components, as well as deterioration in membrane properties such as ion transport and enzyme activity (Ayala et al., 2014). The abundance of polyunsaturated fatty acid in neuronal membranes is a crucial factor contributing to the CNS's vulnerability to oxidative stress (Singh et al., 2019). High susceptibility of the CNS to oxidative stress is also attributed to increased oxygen consumption and neuronal cell antioxidant inadequacy. In the CF+BP group, the improvement of BP-triggered oxidative stress was evidenced by a significant decline in MDA level compared to the BP group. This evidence, as a novel finding, revealed the antioxidant capability of CF on cerebellar tissues.

The present quantitative data indicated that the BP group had significantly decreased number of Purkinje cells than the CON group. This supported our speculation regarding the harmful impact of BP exposure on the rat cerebellar tissues. Neurological problems may result from oxidative damage to crucial macromolecules such lipids, proteins, RNA, and DNA in biological systems (Deepika & Maurya, 2022; Salim, 2017). After Lipid peroxidation, apoptosis may also occur owing to the impairment in the functioning of cell membranes (Pisoschi & Pop, 2015; Sevastre-Berghian et al., 2022). The influence of BP on various physiological systems depends on the dose, exposure route, life stage, and length of exposure (Rubin, 2011). Studies have also revealed that the structure and function of neurons can undergo significant alteration following BP administration (Miyatake et al., 2006).

The CF+BP group had a significantly higher number of Purkinje cells than the BP group, indicating that CF could serve as a protective antioxidant against BP-induced cerebellar change. Since the development and progression of neurological disorders can be impressed by oxidative stress, increasing antioxidant intake may boost oxidative balance and lead to longer and higher quality life (Naureen et al., 2022). CF has been suggested to abolish neural apoptosis via suppressing the caspase-3 expression and improving Bcl-2 expression (Wang et al., 2018). This antioxidant has been proven to mitigate neurodegeneration through suppressing the p38 activity and thereby by downregulation of NF-κB expression (Machado et al., 2018). The neuroprotective potential of CF may also be attributed to its antioxidant activity mediated by Nrf2, which detoxifies ROS (Assis et al., 2014). Furthermore, treatment of CF can help alleviate oxidative damage to mitochondrial DNA (Chavez-Hurtado et al., 2020).

The current study's histopathological analysis exhibited that the BP group's neurons possessed marked structural alteration, which corroborated our stereological findings. It has been documented that BP-induced caspase-3 activation triggers apoptosis, which in turn leads to architectural alteration and cell death (Balci et al., 2020). In the CF+BP group, CF administration exerted an ameliorative efficacy on BP-induced cerebellar tissue destruction, which was consistent with an earlier report (Zhang et al., 2017).

To the best of our knowledge, this is the first experimental examination regarding the potential benefit of CF in reducing BP-induced cerebral tissue abnormality in male rats. Additional research should also be carried out to help preserve cerebellar tissue against environmental pollutants; this could help address public health concerns.

Conclusion

The current study's findings revealed significantly elevated level of MDA, and decrease number of Purkinje cells, as well as architectural alteration in cerebellar tissues exposed to BP. BP-induced excessive ROS generation was suggested as the main factor in pathogenesis of cerebellar alteration via interfering with the antioxidant defence system. Besides, oxidative stress was alleviated following CF treatment, which diminished BP-induced anomalies in cerebellar tissues. This substance as an antioxidant agent may be useful in safeguarding cerebellar tissues exposed to BP.

Declarations

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

Ahmad Yahyazadeh: Conceptualization, Data curation, Funding acquisition, Methodology, Software, Visualization, Investigation, Supervision, Writing – original draft, Writing –review & editing, Validation.

Fatih Mehmet Gür: Data curation, Methodology, Visualization, Writing –review & editing.

Hatice Yaren Kuloğlu: Data curation, Methodology, Visualization, Writing –review & editing.

Ethical Approval

This study was approved by the Laboratory Animal Ethics Committee of Karabuk University (Protocol No. 2023/10/28).

Funding

The research was financially supported by Karabuk University Scientific Research Projects Coordination Unit (KBÜBAP-24-DS-023)

References

Abdou, H. M., Abd Elkader, H. A. E., El-Gendy, A. H., & Eweda, S. M. (2022, Feb). Neurotoxicity and neuroinflammatory effects of bisphenol A in male rats: the neuroprotective role of grape seed proanthocyanidins. *Environ Sci Pollut Res Int, 29*(6), 9257-9268. https://doi.org/10.1007/s11356-021-16311-1

Al-Taee, H., Azimullah, S., Meeran, M. F. N., Alaraj Almheiri, M. K., Al Jasmi, R. A., Tariq, S., Ab Khan, M., Adeghate, E., & Ojha, S. (2019, Sep 5). beta-caryophyllene, a dietary phytocannabinoid attenuates oxidative stress, inflammation, apoptosis and prevents structural alterations of the myocardium against doxorubicin-induced acute cardiotoxicity in rats: An in vitro and in vivo study. *Eur J Pharmacol, 858*, 172467. https://doi.org/10.1016/j.ejphar.2019.172467

Amini, M. R., Sheikhhossein, F., Djafari, F., Jafari, A., Djafarian, K., & Shab-Bidar, S. (2023, Jun). Effects of chromium supplementation on oxidative stress biomarkers. *Int J Vitam Nutr Res, 93*(3), 241-251. https://doi.org/10.1024/0300-9831/a000706

Assis, L. C., Straliotto, M. R., Engel, D., Hort, M. A., Dutra, R. C., & de Bem, A. F. (2014, Oct 24). beta-Caryophyllene protects the C6 glioma cells against glutamate-induced excitotoxicity through the Nrf2 pathway. *Neuroscience, 279*, 220-231. https://doi.org/10.1016/j.neuroscience.2014.08.043

Ayala, A., Munoz, M. F., & Arguelles, S. (2014). Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxid Med Cell Longev, 2014*, 360438. https://doi.org/10.1155/2014/360438

Balci, A., Ozkemahli, G., Erkekoglu, P., Zeybek, N. D., Yersal, N., & Kocer-Gumusel, B. (2020, Jun). Histopathologic, apoptotic and autophagic, effects of prenatal bisphenol A and/or di(2-ethylhexyl) phthalate exposure on prepubertal rat testis. *Environ Sci Pollut Res Int, 27*(16), 20104-20116. https://doi.org/10.1007/s11356-020-08274-6

Chavez-Hurtado, P., Gonzalez-Castaneda, R. E., Beas-Zarate, C., Flores-Soto, M. E., & Viveros-Paredes, J. M. (2020, May). beta-Caryophyllene Reduces DNA Oxidation and the Overexpression of Glial Fibrillary Acidic Protein in the Prefrontal Cortex and Hippocampus of d-Galactose-Induced Aged BALB/c Mice. *J Med Food, 23*(5), 515-522. https://doi.org/10.1089/jmf.2019.0111

Cooper, B. L., & Posnack, N. G. (2022, Mar). Characteristics of Bisphenol Cardiotoxicity: Impaired Excitability, Contractility, and Relaxation. *Cardiovasc Toxicol, 22*(3), 273-280. https://doi.org/10.1007/s12012-022-09719-9

Costa, H. E., & Cairrao, E. (2024, Jan). Effect of bisphenol A on the neurological system: a review update. *Arch Toxicol, 98*(1), 1-73. https://doi.org/10.1007/s00204-023-03614-0

Deepika, & Maurya, P. K. (2022, Dec). Ellagic acid: insight into its protective effects in age-associated disorders. *3 Biotech, 12*(12), 340. https://doi.org/10.1007/s13205-022-03409-7

Khan, J., Salhotra, S., Goswami, P., Akhter, J., Jahan, S., Gupta, S., Sharma, S., Banerjee, B. D., Parvez, S., Gupta, S., & Raisuddin, S. (2019, Dec 1). Bisphenol A triggers axonal injury and myelin degeneration with concomitant neurobehavioral toxicity in C57BL/6J male mice. *Toxicology, 428*, 152299. https://doi.org/10.1016/j.tox.2019.152299

Ma, Y., Liu, H., Wu, J., Yuan, L., Wang, Y., Du, X., Wang, R., Marwa, P. W., Petlulu, P., Chen, X., & Zhang, H. (2019, Sep). The adverse health effects of bisphenol A and related toxicity mechanisms. *Environ Res, 176*, 108575. https://doi.org/10.1016/j.envres.2019.108575

Machado, K. D. C., Islam, M. T., Ali, E. S., Rouf, R., Uddin, S. J., Dev, S., Shilpi, J. A., Shill, M. C., Reza, H. M., Das, A. K., Shaw, S., Mubarak, M. S., Mishra, S. K., & Melo-Cavalcante, A. A. C. (2018, Dec). A systematic review on the neuroprotective perspectives of beta-caryophyllene. *Phytother Res, 32*(12), 2376-2388. https://doi.org/10.1002/ptr.6199

Maniradhan, M., & Calivarathan, L. (2023). Bisphenol A-Induced Endocrine Dysfunction and its Associated Metabolic Disorders. *Endocr Metab Immune Disord Drug Targets, 23*(4), 515-529. https://doi.org/10.2174/1871530322666220928144043

Mannino, F., Pallio, G., Corsaro, R., Minutoli, L., Altavilla, D., Vermiglio, G., Allegra, A., Eid, A. H., Bitto, A., Squadrito, F., & Irrera, N. (2021, Nov 16). Beta-Caryophyllene Exhibits Anti-Proliferative Effects through Apoptosis Induction and Cell Cycle Modulation in Multiple Myeloma Cells. *Cancers (Basel), 13*(22). https://doi.org/10.3390/cancers13225741

Miyatake, M., Miyagawa, K., Mizuo, K., Narita, M., & Suzuki, T. (2006, Jun). Dynamic changes in dopaminergic neurotransmission induced by a low concentration of bisphenol-A in neurones and astrocytes. *J Neuroendocrinol, 18*(6), 434-444. https://doi.org/10.1111/j.1365-2826.2006.01434.x

Naureen, Z., Dhuli, K., Medori, M. C., Caruso, P., Manganotti, P., Chiurazzi, P., & Bertelli, M. (2022, Jun). Dietary supplements in neurological diseases and brain aging. *J Prev Med Hyg, 63*(2 Suppl 3), E174-E188. https://doi.org/10.15167/2421-4248/jpmh2022.63.2S3.2759

Newbold, R. R., Jefferson, W. N., & Padilla-Banks, E. (2009, Jun). Prenatal exposure to bisphenol a at environmentally relevant doses adversely affects the murine female reproductive tract later in life. *Environ Health Perspect, 117*(6), 879-885. https://doi.org/10.1289/ehp.0800045

Pisoschi, A. M., & Pop, A. (2015, Jun 5). The role of antioxidants in the chemistry of oxidative stress: A review. *Eur J Med Chem, 97*, 55-74. https://doi.org/10.1016/j.ejmech.2015.04.040

Refaat, B., & El-Boshy, M. (2022, Apr). Protective antioxidative and anti-inflammatory actions of beta-caryophyllene against sulfasalazine-induced nephrotoxicity in rat. *Exp Biol Med (Maywood), 247*(8), 691-699. https://doi.org/10.1177/15353702211073804

Rubin, B. S. (2011, Oct). Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *J Steroid Biochem Mol Biol, 127*(1-2), 27-34. https://doi.org/10.1016/j.jsbmb.2011.05.002

Salim, S. (2017, Jan). Oxidative Stress and the Central Nervous System. *J Pharmacol Exp Ther, 360*(1), 201-205. https://doi.org/10.1124/jpet.116.237503

Sevastre-Berghian, A. C., Casandra, C., Gheban, D., Olteanu, D., Olanescu Vaida Voevod, M. C., Rogojan, L., Filip, G. A., & Baldea, I. (2022, Dec). Neurotoxicity of Bisphenol A and the Impact of Melatonin Administration on Oxidative Stress, ERK/NF-kB Signaling Pathway, and Behavior in Rats. *Neurotox Res, 40*(6), 1882-1894. https://doi.org/10.1007/s12640-022-00618-z

Singh, A., Kukreti, R., Saso, L., & Kukreti, S. (2019, Apr 22). Oxidative Stress: A Key Modulator in Neurodegenerative Diseases. *Molecules, 24*(8). https://doi.org/10.3390/molecules24081583

Suresh, S., & Vellapandian, C. (2024). Restoring Impaired Neurogenesis and Alleviating Oxidative Stress by Cyanidin against Bisphenol A-induced Neurotoxicity: In Vivo and In Vitro Evidence. *Curr Drug Discov Technol, 21*(2), e250124226256. https://doi.org/10.2174/0115701638280481231228064532

Vanani, A. R., Mahdavinia, M., Shirani, M., Alizadeh, S., & Dehghani, M. A. (2020, May). Protective effects of quercetin against oxidative stress induced by bisphenol-A in rat cardiac mitochondria. *Environ Sci Pollut Res Int, 27*(13), 15093-15102. https://doi.org/10.1007/s11356-020-08048-0

Vandenberg, L. N., Hauser, R., Marcus, M., Olea, N., & Welshons, W. V. (2007, Aug-Sep). Human exposure to bisphenol A (BPA). *Reprod Toxicol, 24*(2), 139-177. https://doi.org/10.1016/j.reprotox.2007.07.010

Wang, G., Ma, W., & Du, J. (2018, Jul). beta-Caryophyllene (BCP) ameliorates MPP+ induced cytotoxicity. *Biomed Pharmacother, 103*, 1086-1091. https://doi.org/10.1016/j.biopha.2018.03.168

Yahyazadeh, A. (2024a). Alteration of Sublingual Gland after Exposure to 6-Mercaptopurine in Male Rat: Potential Efficacy of Propolis. *Meandros Medical And Dental Journal, 25*(1), 12 - 18.

Yahyazadeh, A. (2024b, May 28). The effectiveness of hesperidin on bisphenol A-induced spinal cord toxicity in a diabetic rat model. *Toxicon, 243*, 107724. https://doi.org/10.1016/j.toxicon.2024.107724

Yoshioka, T., Kawada, K., Shimada, T., & Mori, M. (1979, Oct 1). Lipid peroxidation in maternal and cord blood and protective mechanism against activated-oxygen toxicity in the blood. *Am J Obstet Gynecol, 135*(3), 372-376. https://doi.org/10.1016/0002-9378(79)90708-7

Zhang, Q., An, R., Tian, X., Yang, M., Li, M., Lou, J., Xu, L., & Dong, Z. (2017, May). beta-Caryophyllene Pretreatment Alleviates Focal Cerebral Ischemia-Reperfusion Injury by Activating PI3K/Akt Signaling Pathway. *Neurochem Res, 42*(5), 1459-1469. https://doi.org/10.1007/s11064-017-2202-3