

T-P3 HEPATOTOKSIČNI EFEKTI BISFENOLA A, S I F I NJIHOVIH SMEŠA: INTEGRATIVNA *IN SILICO* I *IN VIVO* STUDIJA

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Bisfenol A (BPA), bisfenol S (BPS) i bisfenol F (BPF) su endokrini i reproduktivni ometači koji mogu izazvati oštećenje jetre. Cilj studije bio je da se uporedi toksičnost pojedinačnih bisfenola i njihovih smeša integrativnim *in silico* i *in vivo* pristupom. Zajednički geni povezani sa bisfenolima i oštećenjem jetre identifikovani su u Komparativnoj toksikogenomskoj bazi podataka (CTD). Biomarkeri izdvojeni CytoHubba alatom određeni su kod ženki Wistar pacova subakutno izloženih pojedinačno BPA (0,26 µg/kg t.m./dan), BPS (0,60 µg/kg t.m./dan) i BPF (0,68 µg/kg t.m./dan) i njihovim smešama oralnim putem, u dozama preračunatim na osnovu humane ek-spozicije. Nivoi biomarkera u jetri određeni su ELISA metodom. CTD analizom identifikovana su 192 zajednička gena, među kojima su izdvojeni *IL6*, *TNF*, *IL1B*, *MMP9* i *MCP1*. *In vivo* rezultati pokazali su značajno povećanje *IL1B* u BPF, BPA+BPS i MIX grupama, pri čemu je nivo *IL1B* u MIX grupi bio 1,65 puta viši u odnosu na kontrolu ($p < 0,0001$). *TNF* je pokazao najizraženije povećanje u MIX grupi (54% u odnosu na kontrolu, $p < 0,01$), uz povišene vrednosti u drugim grupama. *IL6* je pokazao suprotan obrazac, sa smanjenjem u BPA+BPS i povećanjem u MIX grupi ($p < 0,05$), dok su *MMP9* i *MCP1* bili promenjeni nakon izlaganja bisfenolima i njihovim smešama, sa najizraženijim efektima u BPF i BPA+BPF grupama. Ove promene ukazuju na poremećaje inflamacije i remodelovanja jetre. Integrativni pristup pokazao je da bisfenoli i njihove smeše utiču na gene/proteine povezane sa oštećenjem jetre, pri čemu su smeše ispoljile izraženije efekte, naročito ternarna smeša, dok je BPF imao najveći potencijal među pojedinačnim bisfenolima.

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T-P3 HEPATOTOXIC EFFECTS OF BISPHENOLS A, S, AND F AND THEIR MIXTURES: AN INTEGRATIVE *IN SILICO* AND *IN VIVO* STUDY

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Bisphenol A (BPA), bisphenol S (BPS), and bisphenol F (BPF) are endocrine and reproductive-disrupting chemicals that may induce liver injury. The aim of this study was to compare the toxicity of individual bisphenols and their mixtures using an integrative *in silico* and *in vivo* approach. Common genes associated with bisphenols and liver injury were identified using the Comparative Toxicogenomics Database (CTD). Biomarkers selected using the CytoHubba algorithm were determined in female Wistar rats sub-acutely exposed orally to BPA (0.26 µg/kg bw/day), BPS (0.60 µg/kg bw/day), and BPF (0.68 µg/kg bw/day), individually and in mixtures, at doses calculated based on human exposure. Liver biomarker levels were determined by ELISA. CTD analysis identified 192 common genes, including *IL6*, *TNF*, *IL1B*, *MMP9*, and *MCP1*. *In vivo* results showed significantly increased *IL1B* levels in the BPF, BPA+BPS, and MIX groups, with *IL1B* in the MIX group being 1.65-fold higher than in controls ($p < 0.0001$). *TNF* showed the most pronounced increase in the MIX group (54% higher than controls, $p < 0.01$), with elevated levels in other groups. *IL6* showed an opposite pattern, decreasing in the BPA+BPS group and increasing in the MIX group ($p < 0.05$). *MMP9* and *MCP1* were altered after bisphenol exposure, with the most pronounced effects in the BPF and BPA+BPF groups. These changes indicate disturbances in inflammation and liver remodeling. Integrative analysis demonstrated that bisphenols and their mixtures affect liver injury-related genes/proteins, with stronger effects of mixtures, particularly the ternary mixture, while BPF showed the highest potential among individual bisphenols.

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