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THE FARNESOID X RECEPTOR AS A POTENTIAL MOLECULAR TARGET FOR PFOA AND PFOS-ASSOCIATED ENDOCRINE AND METABOLIC DYSREGULATION

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Perfluoroalkyl and polyfluoroalkyl substances (PFAS), particularly perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), are persistent environmental contaminants associated with endocrine and metabolic disorders. Due to their high chemical stability, environmental persistence, and bioaccumulation potential, these compounds have been widely detected in water, food, wildlife, and human tissues. Although several toxicological studies have shown associations between PFAS exposure and hepatic, metabolic, and hormonal alterations, the molecular mechanisms underlying their interaction with biological systems remain poorly understood. A clearer understanding of the conformational behavior and intermolecular interactions of PFAS with

biologically relevant targets is therefore essential for elucidating their mechanisms of toxicity and identifying molecular pathways associated with endocrine disruption. In this study, integrated in silico approaches were employed to investigate potential molecular targets associated with the endocrine and metabolic effects of PFOA and PFOS. The molecular structures of both compounds were constructed and geometrically optimized in Avogadro using the MMFF94 force field, followed by semi-empirical refinement using the PM6 method implemented in MOPAC2016. Virtual potential target identification was performed using the SwissTargetPrediction server with Homo sapiens as the reference organism, resulting in 33 candidate targets, from which 11 proteins were selected based on their established involvement in metabolic and hormonal pathways, as reported in the literature. Structural models were retrieved from the PDB and comparative modeling was carried out using the Robetta server, while structural validation was subsequently performed through Ramachandran plot analysis, QMEANDisCo index, and Z-score evaluation using SWISS-MODEL. Molecular docking studies were conducted using Flexible CDOCKER with the CHARMM force field to investigate ligand–protein interactions and identify key binding residues. Molecular dynamics (MD) simulations were performed in Amber2023 under NPT conditions for 200 ns to assess the conformational stability and dynamic behavior of the complexes. Binding free energies were estimated using the MM-PBSA method. Among the 11 targets evaluated, the Farnesoid X Receptor (FXR; PDB: 6HL1, UniProt: Q96RI1) exhibited the highest binding affinity for both compounds. FXR is a nuclear receptor that plays a pivotal role in regulating bile acid, lipid, and glucose homeostasis; its dysregulation is associated with liver dysfunction, dyslipidemia, insulin resistance, and endocrine disruption. Molecular docking indicated favorable binding of PFOA and PFOS to FXR, with key interactions involving amino acid residues Gln216, Tyr184, Lys413, and Arg415 for PFOA, and Gln216, Arg187, and Leu12 for PFOS. MD simulations showed conformational stability of the PFOA–FXR and PFOS–FXR complexes throughout the simulation trajectories and the maintenance of the intermolecular interactions identified during molecular docking. The stability observed for the PFOA–FXR and PFOS–FXR complexes was consistent with the binding free energy estimates, which resulted in a negative value of -20.94 ± 0.25 kcal/mol and -

25.79 ± 0.22 kcal/mol, respectively. These results suggest that FXR constitutes a stable and biologically relevant target for both compounds, indicating a plausible molecular pathway by which PFOA and PFOS exert endocrine and metabolic disruptive effects, and providing a basis for future experimental studies.

Palavras-chave: endocrine disruptors; perfluoroalkyl substances; environmental toxicology; molecular modeling; molecular docking.