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Effects of bisphenol A and its' substitutes on type 2 diabetes mellitus: an *in-silico* study

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Environmental exposure to endocrine disrupting chemicals (EDCs) like bisphenol A (BPA) is increasingly linked to the development of Type 2 Diabetes Mellitus (T2DM). BPA disrupts glucose regulation and insulin signaling, and its structural analogues and derivatives, introduced as substitutes, show similar biological activity. These compounds interact with nuclear receptors such as Estrogen Related Receptor Gamma (ERRγ), a key regulator of energy metabolism, glucose homeostasis and mitochondrial biogenesis, raising concerns about their role in metabolic disorders like T2DM.This study aimed to understand the mechanism of action between BPA and its substitutes under T2DM using in-silico studies, explored through limited research exists and investigates how their binding with metabolic proteins and observe the dynamic structural changes within the receptor-ligand complex. Here the ERRγ maintains an active helix conformation and binds endocrine disruptors, revealing molecular interaction details. Ligands bind mainly to helical regions, forming hydrogen bonds with key amino acid residues located within the LBD, disrupting metabolic expression and contributing to insulin resistance and T2DM.Computational studies were performed using DFT with the B3LYP hybrid exchange correlation function via the basis set 6-31G ++ (d,p) in aqueous phase, to optimize the geometries of the ligands which are structural analogues of BPA. Bisphenol AP (BPAP), Bisphenol P (BPP), Bisphenol BP (BPBP), Bisphenol G (BPG) and Derivatives which are Tetramethyl bisphenol A (TMBPA), Bisphenol TMC (BPTMC), Dinitro bisphenol A (DNBPA) and Nitro BPA (NBPA). Molecular Docking was performed using Autodock4. Calculated values are based on Low Binding Energies to analyze the bonding interactions between receptor-ligand complex. Findings revealed that BPTMC exhibited the highest binding affinity with -10.00 kcal/mol. This has followed by BPP, BPG, BPAP and TMBPA having -8.93 kcal/mol, -8.90 kcal/mol, -8.85 kcal/mol and -8.75 kcal/mol respectively, exhibiting favorable high binding affinities whereas the others were within the expected range. However further molecular dynamic (MD) simulations are required for validating these results. And the bonding interaction analysis focused on identifying Hydrogen bonds between the ligands and active site residues of ERRγ receptor.

Keywords:
BPA, Derivatives, Analogues, Type 2 Diabetes Mellitus, Molecular Docking