Understanding the Xenoestrogenic Activity of BPA Involves Molecular Docking Study with a few Chosen Nuclear Receptors and Toxicodynamics Analysis: An In Silico Research

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Received: 31st January, 2024; Accepted: 6th May, 2024; Published online: 15th May, 2024

https://doi.org/10.33745/ijzi.2024.v10i01.085

Abstract: Bisphenol A (BPA) is predominantly synthesized on a massive scale for use in polycarbonate plastic manufacturing. Because it resembles a hormone, BPA functions as a xenoestrogen, imitating the effects of estrogen in the human reproductive system. Employing the Docking Wizard program on The Molegro virtual Docker system, we molecularly docked BPA onto the 1A52, 1GS4, 2GPU, 5TOA, and 7XTB in order to compare binding energies and gain insight into the toxicodynamics and estrogenic activity of BPA in biological systems. Our investigation clearly shows that BPA’s biggest possibility for coupling is with the estrogen receptor alpha 1A52 (-8.4 Kcal/mol), and then with the ERR-γ receptor 2GPU (-8.4 Kcal/mol). BPA is categorized as an Endocrine Disrupting Chemical (EDC) that can imitate internal hormones and hence, increase the effects they have, or it may hinder with and keep natural hormones from attaching to their targets.

Keywords: Bisphenol A, Xenoestrogen, Toxicodynamics, Endocrine Disrupting Chemical, Biological systems

Citation: Sarkar Diptendu, Mandal Gopal Dev, Kolar Amzad Basha, Roy Tapan Kumar, Jahirhussain G. and Sarasa D.: Understanding the xenoestrogenic activity of BPA involves molecular docking study with a few chosen nuclear receptors and toxicodynamics analysis: An in silico research. Intern. J. Zool. Invest. 10(1): 783-790, 2024.

https://doi.org/10.33745/ijzi.2024.v10i01.085

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**Introduction**

Bisphenol A (BPA) is overwhelmingly manufactured on an enormous basis for usage in polycarbonate-based material manufacturing. Water plastic containers, spectacles, break-resistant windows, and epoxy resins covering a number of metal food packaging, caps on bottles, including water distribution lines are just a few items that include it. There has been much discussion in the media and scientific community about the potential health risks of BPA (Vandenberg *et al.*, 2010). As a xenoestrogen, BPA mimics the actions of estrogen in the body by having characteristics similar to those of a hormone. Despite the relatively small effect, the widespread presence of BPA-containing items is concerning because exposure is essentially lifetime (Melnick *et al.*, 2002). Numerous non-obvious yet often encountered products contain BPA, such as dental fillings, garment designs, shop receipts, and coatings used inside food cans. Public health organizations worldwide and the World Health Organization have both looked into BPA (Angle *et al.*, 2013). Although the usual exposure is below the level now linked to risk, several countries have taken preventative measures to lower exposure, notably by outlawing baby bottles that contain BPA. There is some evidence to suggest that this has reduced newborns’ exposure to BPA. Environmental contaminants of growing concern include BPA. A constant exposure to plant and animal life results from the ongoing release of BPA into the environment, despite its brief half-life and non-bioaccumulating nature (Prins *et al.*, 2018). Even though a lot of research has been done, it frequently uses BPA concentrations far above ambient levels and concentrates on a small number of model organisms (EPA, 1988). Therefore, it is unclear exactly how BPA affects aquatic organisms’ growth, reproduction, and development. Nevertheless, the available information indicates that BPA generally has a negative impact on wildlife (Heindel *et al.*, 2015). Many different types of wildlife seem to be affected by BPA’s effects on development and reproduction; amphibians and invertebrates are two examples of species that seem to be especially vulnerable (FDA, 2018).

Since numerous *in vivo* investigations and testing in the laboratory have demonstrated connections between the consumption of BPA alongside hormone-related malignancies, such as endometrial malignancy, breast, prostate, and ovarian malignancies (Camacho *et al.*, 2019), we have focused *in silico* study on understanding the biological desires of BPA on humans and performing molecular docking on a number of the picked targets.

**Materials and Methods**

**Retrieval of chemical structure of BPA from PubChem:**

The chemical structure of BPA was downloaded along with SMILE from PubChem data base in SDF format (2D) for further study (Heindel *et al.*, 2020).

**Finding Target in Human:**

For finding the target in human, SWISS target (http://www.swisstargetprediction.ch/) was used. Hereafter selecting *Homo sapiens* and providing SMILES predict target was chosen to get various target in human (Sarkar, 2021).

**Selecting and retrieving protein structures from PDB:**

There was total 5 protein structure (ID: 1A52, 1GS4, 2GPU, 5TOA and 7XTB) (Figs. 1-5) selected from PDB (https://www.rcsb.org/) and they were downloaded in PDB format, after looking and analysing SWISS target prediction data. All the selected proteins were nuclear receptor of human. Further energy minimization of all the structures were made by using SPDBV software for docking study (Sarkar *et al.*, 2022).

**Molecular docking study:**

The Molegro virtual docker system’s Docking Wizard is used to handle the Docking procedure (Sarkar and Ganguly, 2022). We can choose which structures to include in the simulation using the
wizard. Next, select the possible binding zone (possible binding pockets are immediately displayed by the software). Following that search, data recording, grouping, and algorithm properties were set up. Inspection of cautions regarding improbable preparations and absent structural details (e.g., unknown residues) helped handle additional limitations. By using rigid, flexible docking, the binding familiarity, ligand competence, and inhibitory possibility to the protein were predicted using the Molegro virtual docker. The BPA structure was imported into mol2 format. The 'Ligand' option was utilized to adjust the torsional branch, non-polar hydrogen ion, charges, and atom type. Together with all of the aforementioned proteins, a created receptor protein grid containing BPA was used for molecular docking.

Results and Discussion

An organic synthetic substance called bisphenol A (BPA) is used as a monomer in the production of polycarbonate plastic. Due to its hormone-like attributes, BPA may attach to receptors that respond to estrogen, therefore may have an effect on weight gain and malignancy. BPA can influence homeostasis and the development of malignant cells by communicating with GPR30 (Sarkar, 2022). Additionally, by connecting to androgen receptors, BPA may disrupt male reproductive function. An online program called Swiss Target Prediction can be employed to forecast the macromolecular domains (human, mouse, and rat protein targets) of bioactive small compounds. This is helpful in predicting unwanted targets, understanding the molecular routes driving a certain phenotypic or their bioactivity, rationalizing the possibility of adverse reactions, and determining whether therapeutic relevant molecules can be repurposed (Sarkar and Maity, 2023). From the SWISS target prediction data in human, we found that 26.7% target was for nuclear receptor, 13.3% for various enzymes, 13.3% for lyase which also a type of enzyme, 13.3% for oxidoreductases, 6.7% for several unclassified proteins, 6.7% of family A G protein-coupled receptors, 6.7% for kinases and 13.3% for ion channels (Fig. 6). This data indicated detrimental effects of BPA and are highlighted by various recent research.

A crucial tool in computerized assistance drug development and structural biological research is molecular docking (Jeng and Watson, 2011). Predicting the main binding mode(s) of a substance that interacts with a protein that has a determined 3-D structure has become the aim of ligand-protein docking. Productive docking techniques include a scoring system that appropriately rates prospective dockings and efficiently explore spaces that are highly dimensional.

Estrogen receptor alpha (ERα), also known as nucleus receptor subfamily 3, subgroup A, the first member (NR3A1), constitutes one of the two main types of receptors that respond to estrogen (Takayanagi et al., 2006). It is a form of nuclear receptor which primarily occurs as a chromatin-binding glycoprotein and is triggered by the sexual hormone estrogen. The alpha estrogen receptor is 1A52. One ligand-activated transcription variable that is necessary for entering hormones, attaching...
DNA, and inducing transcription includes the human estrogen receptor (ER). It is made up of many domains. Multiple ESR1 mRNA transcripts are produced by alternative splicing, and these transcripts mostly differ in their 5-prime untranslated regions (Richter et al., 2007). The docking result revealed that binding energy is -8.4 Kcal/mol which is quite higher and having very strong binding potentiality. Various bonds were found to be involved as van der Waals force, conventional hydrogen bonds, alkyl and covalent bonding (Fig. 7).

The receptor for androgen (AR), also known as nuclei receptor subfamily 3, group C, member 4, is able to attach to any androgenic steroid, including testosterone as well as dihydrotestosterone (Medwid et al., 2018). Androgens cause modest bone development, whereas the estrogen produced during androgen aromatization exhibits a stronger maturity benefit. Teenage steroid users may discover that their growth has been slowed due to high androgen and/or estrogen. Individuals who have low levels of sex hormones during adolescence may grow taller as adults, a condition known as androgen insensitivity syndrome or estrogen insensitivity syndrome (Watson et al., 2007).
1GS4 is an androgen receptor. The docking result revealed that binding energy is -8.2 Kcal/mol which is also quite higher and having very strong binding potentiality. Various bonds were found to be involved as van der Waals force and conventional hydrogen bonds (Fig. 8).

The nucleus receptor designated as estrogen-related receptor gamma, also referred to as nuclear receptor subclass 3, category B, or component 3, is encoded by the human estrogen-related receptor gamma locus (Diamanti-Kandarakis et al., 2009; Sarkar, 2022). Evidence suggests that bisphenol A binds tightly to ERR-γ, acting as a xenoestrogen. BPA appears to bind significantly to ERR-γ, as do its nitrated and chlorinated metabolites. Variations in bisphenol A effects could be explained by varying ERR-γ expression in different body areas. For example, observations of excessive bisphenol A accumulation in the placenta can be explained by the high quantity of ERR-γ discovered there (Zoeller et al., 2012; FDA, 2018). 2GPU is an Estrogen Related Receptor-gamma protein. The docking result revealed that binding energy is -8.4 Kcal/mol which is also quite higher and having very strong binding potentiality. Various bonds were found to be involved as van der Waals force and conventional hydrogen bonds and covalent forces (Fig. 9).

Estrogen receptor beta (ERβ), one of the two main types of receptors that respond to estrogen, has the nuclear receptor that is triggered by the sex steroids estrogen; it has been also known as nuclear receptor subclass 3, category A, individual
In reproductive tissue, ERβ opposes the effects of ERα and may limit cell growth (Camacho et al., 2019). Additionally, ERβ might play a significant part in the lung’s adaptive function during pregnancy (Sarkar, 2021). Prostate along with ovarian carcinomas represent two of the many carcinoma types that are associated with the potent tumor suppressor ERβ. Multiple tissues exhibit ERβ, including the uterus, blood monocytes, tissue macrophages, colonic including bronchial tissue epithelial cells, bladder epithelium, including neoplastic counterparts of these organs. Furthermore, ERβ can be present in many neuron clusters and at varying concentrations throughout the brain (Welshons et al., 2003). 5TOA is a ER beta. The docking result revealed that binding energy is -6.7 Kcal/mol which is also quite higher and having very strong binding potentiality. Various bonds were found to be involved as van der Waals force, alkyl, pi-alkyl, and conventional hydrogen bonds and covalent forces (Fig. 10).

The 5HT protein that has engaged the native serotonin i.e., 5-hydroxytryptamine, is a receptor associated with G proteins that enhances excitation neurological communication which has been connected to s subunit of G (Zoeller et al., 2014). This was previously demonstrated that while central 5HT6 receptor activation improves GABAergic transmission across the central nervous system, receptor blockage boosts glutamatergic along with cholinergic neurological communication across different brain regions.
Whenever 5HT6 receptor opposition behavior prevails, more dopamine as well as norepinephrine accumulate in the temporal cortex, but excitation exerts the opposite impact (Vandenberg et al., 2012). 7XTB is a Serotonin 6 (5-HT6) receptor. The docking result revealed that binding energy is -6.4 Kcal/mol which is also quite higher and having very strong binding potentiality. Various bonds were found to be involved as van der Waals force conventional hydrogen bonds and covalent forces (Fig. 11).

The detrimental effects of BPA upon health have been extensively addressed in both the scholarly and public arenas (Heindel et al., 2015). Since BPA is lipophilic, it might build up in a range of individuals and animal tissues, impairing physiology along with posing a health risk (logP value of 3.4). Actually, studies conducted on cell cultures, humans as well as animals suggest that this material may contribute to overweight in a number of ways. By altering PPARs, BPA promotes fatty tissue development, raises the level of lipids in the liver and adipose tissue, and changes cytokine output (Sarkar et al., 2022, Sarkar and Maity, 2023). Furthermore, data derived from human and other cell lines show that BPA interferes with thyroid hormone production, secretion, and transmission (Watson et al., 2005). In addition to its anti-androgenic qualities, on estrogen receptors, BPA operates as a stimulant; upon androgen receptors, on the other hand, it operates as a depressant. Its estrogen-like activity is the primary reason for worries, even though it can also operate as a hormone disruption agent by interacting through various receptor systems (Sarkar et al., 2022). Being exposed to BPA is effectively lifelong exposure, even though these interactions are extremely rare, which prompts concerns about probable cumulative consequences (Camacho et al., 2019). Since numerous research studies are being conducted on this kind for a long time low-dose conversation, it has been shown that the impacts seen plus the quantities at which they appear vary markedly from one to the other.

**Conclusion**

We used The Molegro virtual docker system’s Docking Wizard software to molecularly dock BPA onto the 1A52, 1GS4, 2GPU, 5TOA, and 7XTB in order to assess the binding energies amongst all of them in order to better figure out the toxicodynamics along with estrogenic behavior of BPA in biological tissues. It is evident from our research that BPA has the greatest propensity for interaction with the estrogen receptor alpha, 1A52 (-8.4 Kcal/mol), and then the ERR-γ receptor, 2GPU (-8.4 Kcal/mol). Endocrine destabilizing chemicals, such as BPA, have been found to interact with or hinder natural hormones from attaching to their sites. They can additionally imitate hormones, amplifying the impacts of endogenous hormones.

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