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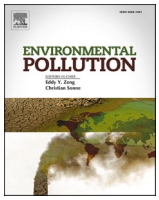

Structural insight into the mechanisms and interacting features of endocrine disruptor Bisphenol A and its analogs with human estrogen-related receptor gamma☆

Rajesh Kumar Pathak, Jun-Mo Kim *

Department of Animal Science and Technology, Chung-Ang University, Anseong-si, Gyeonggi-do 17546, Republic of Korea

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ABSTRACT

Bisphenol A (BPA) is a very important chemical from the commercial perspective. Many useful products are made from it, so its production is increasing day by day. It is widely known that Bisphenol A (BPA) and its analogs are present in the environment and that they enter our body through various routes on a daily basis as we use things made of this chemical in our daily lives. BPA has already been reported to be an endocrine disruptor. Studies have shown that BPA binds strongly to the human estrogen-related receptor gamma (ERRγ) and is an important target of it. This study seeks to understand how it interacts with ERRγ. Molecular docking of BPA and its analogs with ERRγ was performed, and estradiol was taken as a reference. Then, physico-chemical and toxicological analysis of BPA compounds was performed. Subsequently, the dynamic behavior of ERRγ and ERRγ-BPA compound complexes was studied by molecular dynamics simulations over 500 ns, and using this simulated data, their binding energies were again calculated using the MM-PBSA method. We observed that the binding affinity of BPA and its analogs was much higher than that of estradiol, and apart from being toxic, they can be easily absorbed in our body as their physicochemical properties are similar to those of oral medicines. Therefore, this study facilitates the understanding of the structure–activity relationship of ERRγ and BPA compounds and provides information about the key amino acid residues of ERRγ that interact with BPA compounds, which can be helpful to design competitive inhibitors so that we can interrupt the interaction of BPA with ERRγ. In addition, it provides information on BPA and its analogs and will also be helpful in developing new therapeutics.

1. Introduction

As some of the primary raw materials used in the manufacture of polycarbonate plastics, Bisphenol A (BPA) and its analogs have a crucial impact on our daily lives (Wang et al., 2020). The production of many everyday consumer goods, including food packaging materials, toys, thermal paper, automotive lenses, building materials, and encapsulations of electrical and electronic components, primarily uses BPA and its analogs (Huang et al., 2012; Wang et al., 2020). BPA-based products are very popular among consumers and are now an essential part of society. According to reports, residual BPA can be easily released from a variety of products, contaminating the environment and food (Akhbarizadeh et al., 2020; Rahman et al., 2021). As a result, it is very common for humans to be exposed to this chemical through the oral, transdermal, and respiratory routes; evidence of this exposure can be found in a variety of biological samples including urine, milk, blood, serum, plasma, hair, saliva, sweat, placenta, and amniotic fluid (Akhbarizadeh et al., 2020; Beausoleil et al., 2018; Martinez et al., 2021; Rahman et al., 2021; Tschersich et al., 2021; Vandenberg et al., 2010; Vorkamp et al., 2021).

BPA and its analogs are reported to be endocrine disruptors, responsible for several diseases in human and animals such as reproductive abnormalities, metabolic diseases, neurobehavioral disorders, developmental disorder, and cancers. They are also harmful to the environment (Ma et al., 2019; Mustieles et al., 2020; Rahman et al., 2021; Siracusa et al., 2018). One of the most critical periods for the potential of endocrine disruption is during pregnancy, as it can have impacts for future generations (Rolfo et al., 2020). Research has shown that bisphenols are detectable in the placenta and amniotic fluid of pregnant women. These chemicals can have a negative impact on fetal

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* Corresponding author.
E-mail addresses: rkpathak@cau.ac.kr (R.K. Pathak), junmokim@cau.ac.kr, junmokim@cau.ac.kr (J.-M. Kim).

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and placental health by interfering with the development of the embryonic epigenome. Such interference could potentially contribute to the development of health issues later in life (Lorigo and Cairrao, 2022; Rolfo et al., 2020; Tang et al., 2020). There is also great concern regarding the effects of BPA and its analogs on the cardiovascular system, responsible for several diseases such as diabetes, obesity, blood pressure deregulation, and other cardiovascular diseases (Abrantes--Soares et al., 2022; Cooper and Posnack, 2022; Fonseca et al., 2022; Ramadan et al., 2020). Unfortunately, human dependency on BPA products makes it challenging task to reduce its use and mitigate its harmful effects. No safer and cheaper alternative to BPA has yet been found (Eladak et al., 2015). To prevent toxicity, it may be best to reduce the use of BPA in daily life until viable alternatives become available (Rahman et al., 2021).

Studies have found that BPA binds strongly to human estrogen-related receptor gamma (ERRγ) in comparison to estrogen receptor (ER) itself (Li et al., 2015; Liu et al., 2010; Matsushima et al., 2007). ERRγ is an orphan nuclear receptor closely related to ER. Three distinct ERR proteins (α, β, γ) have so far been discovered (Matsushima et al., 2007; Xue et al., 2019). In rodents and humans, this receptor is expressed at high levels in fetal brains as well as other tissues (Cheung et al., 2005; Takeda et al., 2009). However, numerous BPA analogs were found in different biological samples, and it was observed that their effects are similar to BPA (Rahman et al., 2021; Vorkamp et al., 2021). Since ERRγ is involved in the regulation of energy metabolism and mitochondrial function, it has been seen in animal models that ERRγ serves as a downstream mediator of multiple extracellular signals, playing an important role in endocrine and metabolic signaling (Misra et al., 2017). Thus, dysregulation of ERRγ contribute to development of metabolic disorders like hyperglycemia, insulin resistance, and damage to the liver due to alcohol consumption. Besides, it also concerned in responses to the bacterial infection (Kim and Choi, 2019; Misra et al., 2017). The binding of BPA with ERRγ was demonstrated in order to understand its toxicodynamics and estrogenic activity on the biological systems (Babu et al., 2012; Matsushima et al., 2007).The frequent use of BPA analogs in industries and its harmful effect on health and environment have recently attracted global attention in order to find solutions (Ohore and Zhang, 2019; Rahman et al., 2021). Based on various abnormalities associated with ERRγ due to its interaction with BPA, it can be utilized for further research (Babu et al., 2012; Misra et al., 2017).

In light of the aforementioned facts, it is crucial to investigate the mechanisms and interactions between BPA analogs and ERRγ, as well as their pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics (toxicity). To achieve this, we conducted molecular docking studies involving 22 BPA analogs, including BPA itself. The naturally synthesized hormone estradiol was taken as reference. Our objective was to assess their binding energy and identify the interacting amino acid residues.

We selected the top ten compounds that exhibited strong binding affinity with ERRγ, as well as the estradiol, for further analysis. This analysis included ADMET prediction, molecular dynamics simulations, and Gibbs free energy landscape analysis. Additionally, we calculated the binding free energy of the selected compounds using molecular dynamics simulation data through the MM-PBSA method. Our investigation also deciphered the interaction mechanisms of each compound, identified the amino acid residues of ERRγ contributing to the binding with BPA analogs, and estimated their binding free energies. These findings will enhance our understanding of ERRγ–BPA and its analogs' interactions, potentially guiding the development of novel competitive inhibitors using structure-based drug discovery approaches.

2. Materials and methods

2.1. Dataset of BPA and its analogs and target protein structure

Literature studies led us to select the 3D structure of BPA and its analogs (n = 22), as well as estradiol, which were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in the structure-data file format (SDF) (Babu et al., 2012; Irwin and Shoichet, 2005; Rahman et al., 2021), and OpenBabel (https://openbabel.org/wiki/Main_Page) was employed to convert all the compounds into PDBQT (Protein Data Bank (PDB), partial charge (Q), and atom type (T)) files. The co-crystallized structure of ERRγ with BPA (PDB ID: 2E2R) was retrieved from the PDB database (https://www.rcsb.org). The protein structure was visualized and prepared with UCSF Chimera by removing all non-standard residues and co-crystallized ligand BPA (Matsushima et al., 2007). A PDBQT file of the target protein was then generated using AutoDock tools by adding charges and polar hydrogens. This was followed by generating the grid box size that incorporated the binding cavity of the co-crystallized ligand. The grid dimensions were set to 40 × 40 × 40 Å for the x, y, and z dimensions, and the center coordinates were set to −15.913, −4.646, and −29.766 Å for the x, y, and z axes, respectively. Furthermore, the docking parameters were validated by redocking the co-crystalized ligand on its receptor using AutoDock Vina (Eberhardt et al., 2021; Matsushima et al., 2007; Trott and Olson, 2010). The predicted root-mean-square deviation (RMSD) value between the co-crystallized ligand (BPA) and its re-docked conformation was 1.127 Å, calculated using PyMOL (https://pymol.org/2/).

2.2. Molecular docking

Molecular docking is used in identification of low-energy binding modes of a ligand, within an active site of a receptor (Pathak et al., 2020). It is a computational technique widely used in the identification of lead compounds (Pant et al., 2022). Molecular docking software AutoDock Vina finds the best relative orientation for a ligand when docking with a molecular target and offers a protein–ligand complex structure with the lowest binding energy (Trott and Olson, 2010). Here, molecular docking studies of BPA, BPA analogs, and estradiol with ERRγ were performed using AutoDock Vina (Trott and Olson, 2010). The protein–ligand complex were generated using UCSF Chimera for visualization and analysis (Pettersen et al., 2004). Furthermore, protein–ligand interaction diagrams in 2D and 3D were plotted by Discovery Studio Visualizer (https://discover.3ds.com/discovery-studio-visualizer-download) to determine the key amino acid residues contributed to the binding via various types of interactions.

2.3. Physicochemical properties analysis and toxicity prediction

The physicochemical properties and toxicity of the top ten BPA compounds showing higher affinity with ERRγ and reference estradiol were analyzed. The PubChem database (https://pubchem.ncbi.nlm.nih.gov/) provided information on the molecular weight, LogP, H-bond donor and acceptor, as well as the topological surface area of each compound. In addition, OSIRIS Property Explorer (https://www.organic-chemistry.org/prog/peo/) predicted the toxic properties of the compound, including mutagenic, tumorigenic, and irritant properties. Furthermore, Canonical SMILES notations of the top-ten screened BPA compounds and Estradiol retrieved from PubChem were subjected to pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) for the prediction of various pharmacokinetic properties, including absorption (Water solubility and intestinal absorption), distribution (Blood–brain barrier (BBB) permeability and Central nervous system (CNS) permeability), metabolism (CYP2D6 substrate, CYP3A4 substrate, and CYP1A2 inhibitor), excretion (total clearance), and toxicity (AMES toxicity and oral rat acute toxicity) (Pires et al., 2015).

2.4. MD simulations

The top ten BPA compound–ERRγ complex based on binding free energy, estradiol–ERRγ complex, and ERRγ were chosen for molecular dynamics (MD) simulation. The MD simulation was executed using GPU

accelerated GROMACS package version 2018.1(Abraham et al., 2015; Pall et al., 2020). The system was prepared in accordance with previous research (Pathak et al., 2022a; Pathak et al., 2022b; Pathak et al., 2022c). PRODRG was used to generate the ligand topology (Schuttelkopf and van Aalten, 2004), while pdb2gmx was used to generate the protein topology (Oostenbrink et al., 2004). Solvation was performed with the simple point charge water model. In order to construct topologies of protein–ligand complexes, generated protein and ligand topologies were merged. A cube-shaped box was generated, and complex was placed inside it. Through the use of Na^+ and Cl^- ions, electroneutrality was preserved for the system. Furthermore, the steepest descent minimization algorithm was used to minimize the energy of protein and protein–ligand complexes. The system was equilibrated using NVT and NPT to maintain volume, temperature, and pressure. Finally, all systems were subjected for 500-ns simulation time and coordinates were saved at 2-fs intervals. Structural stability of protein and protein–ligand complexes was assessed using root-mean-square deviation (RMSD), flexibility using root-mean-square fluctuation (RMSF), compactness analysis using a radius of gyration (Rg), protein folding and stability using solvent-accessible surface area (SASA) analysis, protein–ligand interactions using hydrogen bond analysis, and structural motions through principal component analysis (PCA) using GROMACS (https://www.gromacs.org/) utilities gmx 'rms', 'rmsf', 'gyrate', 'sasa', 'hbond', 'covar', and 'anaeig' respectively. For graphical analysis and visualization, the 2D plotting program Grace (https://plasma-gate.weizmann.ac.il/Grace/) was used.

2.5. Free energy landscape and binding energy calculation

The free energy landscape analysis (FEL) was used to determine the minima states of protein and protein–ligand complexes. The FEL was calculated using a GROMACS utility called 'gmx sham'. The g_mmpbsa tool was used to compute binding free energy of selected BPA compound–ERRγ complexes and estradiol–ERRγ complexes based on the produced high-throughput MD simulation data (Kumari et al., 2014). A protein–ligand complex's binding energy ($G_{binding}$) can be expressed as

$$\Delta G_{binding} = G_{complex} - \left(G_{protein} + G_{ligand}\right)$$

Here, $G_{complex}$ represents the total binding free energy of the complex, $G_{protein}$ represents an unbound receptor, and G_{ligand} represents an unbound ligand, respectively. The contribution of amino acid residue 'x' energy involved in an interaction was computed as:

$$\Delta R_x^{BE} = \sum_{i=0}^{n} \left(A_i^{bound} - A_i^{free}\right),$$

where n denotes the total number of residues, and A_i^{bound} and A_i^{free} represent the energy of the ith atom for each 'x' residue.

3. Results

3.1. Investigating the binding energy of BPA compounds against ERRγ with respect to estradiol

A molecular docking technique can be used to discover the best intermolecular framework between macromolecular targets and ligands. In order to form a complex, it predicts which ligand will interact with the target and determines the binding energy among them. Existing studies decipher the interacting features of endocrine disruptor BPA and its analogs with Human ERRγ. The binding energy of estradiol with ERRγ was also estimated to evaluate the binding affinity of the BPA compound. In general, protein–ligand complexes with low binding energies have high binding affinity. Therefore, the top ten BPA compounds exhibiting minimum binding energy with ERRγ were selected for further analysis along with estradiol as reference. The names of BPA compounds, reference estradiol, their PubChem id, Chemical Abstracts Service (CAS) registry number, binding free energy, and interacting amino acid that contributed to the interactions are listed in Table 1.

3.2. Evaluation and visualization of top hits BPA compounds with ERRγ

In molecular docking, the binding free energy of the compound interacting with the macromolecular target is used to categorize the best interacting compounds. Among 22 BPA compounds, the top ten were selected (binding energy range: −10.8 to −8.8 kcal/mol) along with estradiol to determine their binding nature with ERRγ. The reference compound estradiol was found to form one alkyl bond with amino acid residue PRO246; one pi-sulfur bond with GLU245; one pi-alkyl bond with LYS248; one alkyl bond each with ARG316 and PHE366 of ERRγ with binding free energy of −7.5 kcal/mol (Fig. 1A and B). In addition, among BPA compounds, Bisphenol AF was found to form one conventional hydrogen bond and one pi-sigma bond with LEU309 with one conventional hydrogen bond and one pi-sigma bond; one alkyl, pi-alkyl, and halogen bond with LEU268; one alkyl and pi-alkyl bond with ALA272; one alkyl and pi-sulfur bond with MET306; one pi-alkyl bond with VAL313; one pi-pi stacked and pi-pi t-shaped bond with TYR326; one pi-alkyl bond with LEU342; and two alkyl bonds with PHE435 with ERRγ, and a binding free energy of−10.8 kcal/mol (Fig. 1C and D). Bisphenol Z interacts with LEU309 through one conventional hydrogen bond and pi-sigma bond; one conventional hydrogen bond with ARG316 and ASN346; one pi-alkyl bond with LEU268, CYS269, VAL313, LEU342, PHE435, and PHE450; two pi-alkyl bonds with ALA272; one pi-sulfur bond with MET306, and one pi-pi stacked and one pi-pi t-shaped bond with TYR326 of ERRγ with binding free energy −10.4 kcal/mol (Fig. 1E and F). Bisphenol B interacts with GLU275 and ASN346 through one conventional hydrogen bond, forming one alkyl bond with LEU268, CYS269, and PHE450; one alkyl and one pi-alkyl bond with ALA272; one pi-alkyl bond with LEU309, VAL313 and LEU342; one pi-pi stacked and pi-pi t-shaped bond with TYR326; one pi-sulfur bond with MET306, and one pi-sigma bond with PHE435 of ERRγ with binding free energy −10.1 kcal/mol (Fig. 1G and H).Bisphenol A interacts with LEU309 and ARG316 through one conventional hydrogen bond; one pi-sulfur bond with MET306; one pi-alkyl bond with LEU268, ALA272,VAL313,and LEU342; and formed pi-pi stacked and pi-pi t-shaped bond with TYR326 of ERRγ with binding free energy −9.9 kcal/mol (Fig. 1I and J). Bisphenol E interacts with LEU309 with one conventional hydrogen bond and pi-sigma bond and formed one conventional hydrogen bond with ASN346; it formed a pi-alkyl bond with ALA272, VAL313, LEU342, and ALA431; one pi-sulfur bond with MET306; one unfavorable acceptor-acceptor bond with GLU275, and one pi-pi stacked and pi-pi t-shaped bond with TYR326 of ERRγ with binding free energy −9.5 kcal/mol (Fig. 2A and B). Bisphenol PH binds with amino acid residues PRO246, ILE279, and VAL325 with pi-alkyl bonds; forming pi-alkyl, pi-cation, and pi-anion bonds with LYS248 and ARG316; and pi-cation and pi-anion bonds with GLU275 and LYS370 of ERRγ with binding free energy −9.3 kcal/mol (Fig. 2C and D). BTUM interacts with ASP273 with two conventional hydrogen bonds; ASP254 with one conventional hydrogen bond; LYS448 with one conventional hydrogen bond and one pi-alkyl bonds; LEU449 with one conventional hydrogen bond, one pi-alkyl bond and one alkyl bond; forming one pi-alkyl bond withLYS263 and ARG274; one pi-anion bond with ASP270; one pi-sigma and one alkyl bond with VAL257, and one unfavorable acceptor–acceptor bond with THR267 of ERRγ with binding free energy −9.3 kcal/mol (Fig. 2E and F). MBHA interacts with GLU275 through one conventional hydrogen bond; forming pi-alkyl bond with LEU268, ALA272, LEU309, VAL313 and LEU342; one sulfur-x and one pi-sulfur bond with MET306; and one pi-pi stacked and pi-pi t-shaped bond withTYR326 of ERRγ with binding free energy −9.2 kcal/mol (Fig. 2G and H). Bisphenol F interacts with LEU309 via one conventional hydrogen bond and one pi-sigma bond; one pi-alkyl bond each with ALA272, VAL313, ALA431, and LEU342; one pi-sulfur bond with MET306, and pi-pi stacked and pi-pi t-

Table 1
List of docked BPA compounds and Estradiol, their binding free energies, and interacting amino acid residues of the Human ERRγ. The amino acid residues in bold indicate the residues involved in interactions via conventional hydrogen bonds.

S. No.	BPA and its analogs	PubChem (CID)	CAS	Binding energy (Kcal/mol)	Amino acid residues involved in interaction
1.	**Estradiol**	**5757**	**50–28–2**	**−7.5**	PRO246, GLU245, LYS248, ARG316, PHE366
2.	Bisphenol AF	73864	1478-61-1	−10.8	LEU268, ALA272, MET306, **LEU309,** VAL313, TYR326, LEU342, PHE435
3.	Bisphenol Z	232446	843-55-0	−10.4	LEU268, CYS269, ALA272, MET306, **LEU309,** VAL313, **ARG316,** TYR326, LEU342, PHE435, **ASN346,** PHE450
4.	Bisphenol B	66166	77-40-7	−10.1	LEU268, CYS269, ALA272, **GLU275**, MET306, LEU309, VAL313, TYR326, PHE435, LEU342, **ASN346,** PHE450,
5.	Bisphenol A (BPA)	6623	80-05-7	−9.9	LEU268, ALA272, **LEU309,** MET306, VAL313, **ARG316,** TYR326, LEU342
6.	Bisphenol E	608116	2081-08-5	−9.5	ALA272, GLU275, MET306, **LEU309,** VAL313, TYR326, LEU342, ALA431, **ASN346**
7.	Bisphenol PH	13059052	24038-68-4	−9.3	PRO246, LYS248, GLU275, ILE279, ARG316, VAL325, LYS370
8.	BTUM	3596056	151882-81-4	−9.3	**ASP254,** VAL257, LYS263, THR267, ASP270, **ASP273,** ARG274, **LYS448, LEU449**
9.	MBHA	78805	5129-00-0	−9.2	LEU268, ALA272, **GLU275,** MET306, LEU309, VAL313, TYR326, LEU342
10.	Bisphenol F	12111	620-92-8	−8.9	ALA272, MET306, **LEU309,** VAL313, TYR326, ALA431, LEU342
11.	2,4-BPS	79381	5397-34-2	−8.8	ALA272, **GLU275,** MET306, LEU309, VAL313, TYR326, ALA431, LEU342, LEU345
12.	4-((4-(Benzyloxy) phenyl)sulfonyl) phenol	113063	63134-33-8	−8.8	GLU245, PRO246, LYS248, GLU275, VAL278, ILE279, TYR315, ARG316, **LYS363**
13.	3-(3-Tosylureido) phenyl p-toluenesulfonate	22035425	232938-43-1	−8.7	PRO246, LYS248, GLU275, VAL278, ILE279, TYR315, **ARG316**, LEU318, LYS363
14.	Bisphenol A bis (diphenyl phosphate)	9874825	5945-33-5	−8.4	TYR250, MET252, PRO253, PRO255, ASP259, LYS263, ALA264, ASP329, TYR330, **GLN336**, LEU339, ALA340
15.	2,2′-Bisphenol F	75575	2467-02-9	−8.3	ALA272, MET306, LEU309, VAL313, TYR326, LEU342, LEU345, ALA431
16.	Bisphenol P	630355	2167-51-3	−7.6	VAL432, TYR436, **ARG425,** THR429, VAL458
17.	2,2-Bis(4-hydroxy-3,5-dimethylphenyl) propane	79717	5613-46-7	−7.5	LEU268, LEU271, ALA272, MET306,

(*continued on next page*)

Table 1 (*continued*)

S. No.	BPA and its analogs	PubChem (CID)	CAS	Binding energy (Kcal/mol)	Amino acid residues involved in interaction
					LEU309, VAL313, **TYR326,** ALA431, PHE435, LEU342, ASN346
18.	Bisphenol AP	623849	1571-75-1	−7.4	GLU245, LYS248, ARG316, LYS363
19.	Phenol, 4,4′-sulfonylbis[2-(2-propenyl)	833466	41481-66-7	−7.4	GLU245, LYS248, ILE249, TYR315, **ARG316,** LEU318, **LYS363**
20.	2,2-Bis(4-hydroxy-3-methylphenyl) propane	6620	79-97-0	−7.4	LYS248, ILE249, LEU271, ILE279, ILE308, LEU309, **GLY312**, ARG316, ALA327, LYS370
21.	4-((4-Isopropoxyphenyl) sulfonyl)phenol	9904141	95235-30-6	−7.1	GLU245, LYS248, TYR315, ARG316, **LYS363**
22.	4-((4-(Allyloxy) phenyl)sulfonyl) phenol	2054598	97042-18-7	−6.9	GLU245, LYS248, ILE279, TYR315, ARG316, **LYS363,** LYS370
23.	Bis[2-(p-hydroxyphenylthio) ethoxy]methane	3086375	93589-69-6	−5.9	PRO246, LYS248, GLU275, ARG316, **LEU318, SER319,** PHE366

shaped bonds with TYR326 of ERRγ with binding free energy −8.9 kcal/mol (Fig. 2I and J). 2,4-BPS interacts with GLU275 via one conventional hydrogen bond; one pi-alkyl bond each with ALA272, VAL313, LEU342, LEU345 and ALA431; one pi-sulfur bond with MET306; one pi-sigma bond with LEU309, and pi-pi stacked and pi-pi t-shaped bonds with TYR326 of ERRγ with binding free energy −8.8 kcal/mol (Fig. 2K and L).

3.3. Assessment of physicochemical properties and toxicity of BPA compounds

The physicochemical properties of the top ten selected BPA compounds were analyzed and compared with reference estradiol. Eight principal descriptors, i.e., molecular weight, LogP, hydrogen bond donor, hydrogen bond acceptor, topological polar surface area, and mutagenic, tumorigenic, and irritant properties were included in the studies. Molecular weight, LogP, hydrogen bond donor, hydrogen bond acceptor, and topological polar surface area data of compounds were mined from PubChem. Toxicology predictions, i.e., mutagenic, tumorigenic, and irritant properties were evaluated using the OSIRIS Property Explorer tool. Based on our analysis, BPA compounds follow the Lipinski's rule of five except for Bisphenol Z (LogP 5.4), Bisphenol PH (LogP 7.3), and BTUM (Molecular weight 592.7). Their behavior is like an oral drug, so they easily get absorbed in the body of humans and animals. They also possessed polar surface areas <140 $Å^2$, indicating high cell membrane permeability, except for BTUM. During toxicity prediction, mutagenic and tumorigenic properties were observed in Bisphenol B and BTUM. Furthermore, an irritant property was predicted in the top ten selected BPA compounds except BTUM, MBHA, and Bisphenol F. The results obtained during the physicochemical properties and toxicity analyses are presented in Table 2. Additionally, pharmacokinetic properties were predicted using pkCSM. In absorption prediction, two important parameters are water solubility and intestinal absorption, which were estimated to fall within the range of −4.566 to −2.87 log mol/L and 70.04%–95.423% for BPA compounds, and −3.803 log mol/L and 93.898% for Estradiol, respectively. In distribution, predictions were made for BBB permeability and CNS permeability, ranging from −1.171 to 0.395 log BB and −2.979 to −0.564 log PS for BPA compounds, and −0.072 log BB and −1.33 log PS for Estradiol. In metabolism analysis, parameters for CYP2D6 substrate, CYP3A4 substrate, and CYP1A2 inhibitor were examined. All selected BPA compounds, including Estradiol, were predicted to be 'No' for CYP2D6 substrate, while all except MBHA and 2,4-BPS were predicted to be 'Yes' for CYP3A4 substrate. For CYP1A2 inhibitor, all were predicted to be 'Yes' except for BTUM. In excretion, total clearance was estimated in the range of −0.293 to 0.574 log ml/min/kg for BPA compounds and 0.784 log ml/min/kg for Estradiol. In terms of toxicity, predictions were made for AMES toxicity, oral rat acute toxicity, and oral rat chronic toxicity parameters. AMES toxicity was predicted as 'No' for all compounds except Bisphenol PH and MBHA. Furthermore, oral rat acute toxicity and chronic toxicity values were estimated to range from 2.126 to 3.106 mol/kg and 1.037 to 2.405 log mg/kg_bw/day for BPA compounds, and 2.697 mol/kg and 1.953 log mg/kg_bw/day for Estradiol, respectively (Table S1).

3.4. Structural and conformational analysis of the unbound and bound systems of ERRγ using MD simulation

An MD simulation of the ERRγ was performed to visualize its dynamic behavior before (unbound) and after (bound) binding with BPA compounds and reference estradiol. The results were summarized using diverse parameters such as RMSD, RMSF, Rg, SASA, H-bond, PCA, FEL, and binding free energy calculations.

3.4.1. Conformational stability analysis

Protein conformational stability was measured by the RMSD during MD simulation of their structure. A structure with a lower RMSD value is more stable than one with a higher RMSD value. In this case, we have calculated the RMSD value over a period of 500 ns. This represents the deviation from the first to the next and subsequent structures. The ERRγ, as well as all complexes, exhibited low RMSD values based on the RMSD plot of backbone c-alpha atoms. The average RMSD of ERRγ was calculated as 0.25 nm. However, the RMSD values of the ERRγ–estradiol, ERRγ–Bisphenol AF, ERRγ–Bisphenol Z, ERRγ–Bisphenol B, ERRγ–Bisphenol A, ERRγ–Bisphenol E, ERRγ–Bisphenol PH, ERRγ–BTUM, ERRγ–MBHA, ERRγ–Bisphenol F, and ERRγ–2,4-BPS complexes were 0.35, 0.31, 0.36, 0.36, 0.35, 0.38, 0.32, 0.28, 0.27, 0.30, and 0.35 nm, respectively. During the simulation, all systems were predicted to establish themselves and form a stable complex (Fig. 3A).

3.4.2. Flexibility and residual mobility analysis

In RMSF analysis, protein properties can be accessed by demonstrating their flexibility residual mobility. We therefore examined the RMSF of the ERRγ and its complexes over a period of 500 ns. The average RMSF value of the ERRγ was measured as 0.16 nm. However, the RMSF values of the ERRγ–estradiol, ERRγ–Bisphenol AF,

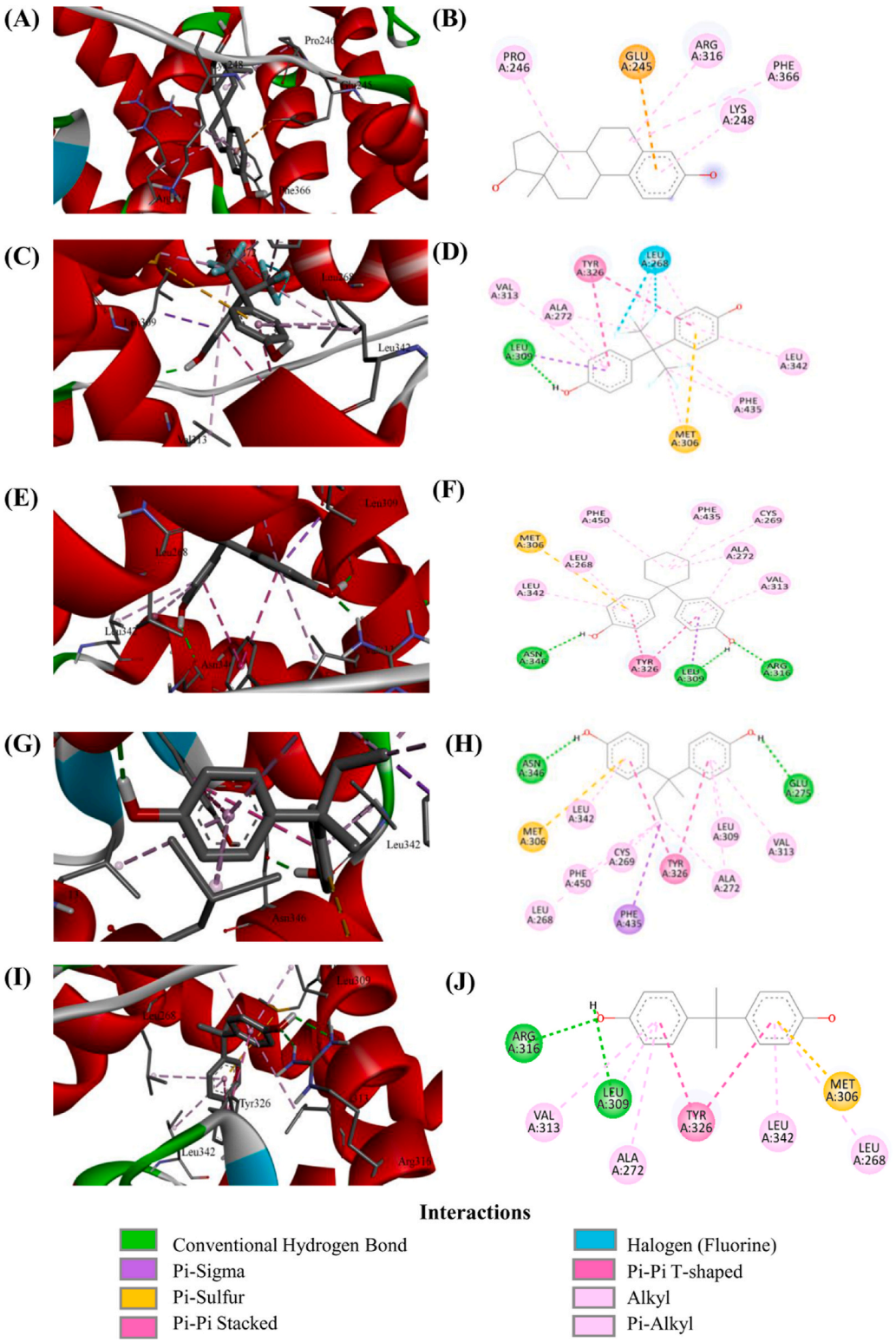

Fig. 1. 3D and 2D representations of the binding interactions of BPA compounds and reference estradiol with human ERRγ depicted key amino acid residues that contributed to protein–ligand interactions **(A-B)** Estradiol, **(C–D)** Bisphenol AF, **(E–F)** Bisphenol Z, **(G–H)** Bisphenol B, **(I–J)** Bisphenol A.

ERRγ–Bisphenol Z, ERRγ–Bisphenol B, ERRγ–Bisphenol A, ERRγ–Bisphenol E, ERRγ–Bisphenol PH, ERRγ–BTUM, ERRγ–MBHA, ERRγ–Bisphenol F, and ERRγ–2,4-BPS complexes were 0.15, 0.18, 0.15,0.17, 0.17, 0.19, 0.13, 0.15, 0.15, 0.16, and 0.17 nm, respectively (Fig. 3B).

3.4.3. Compactness analysis

In order to understand how protein structure compactness, stability, and folding change over time, Rg values can be calculated. As a measure of structural compactness, Rg values were calculated for the ERRγ and their complexes. The average Rg values were calculated as 1.74 nm for ERRγ. Furthermore, the average Rg values of the ERRγ–estradiol,

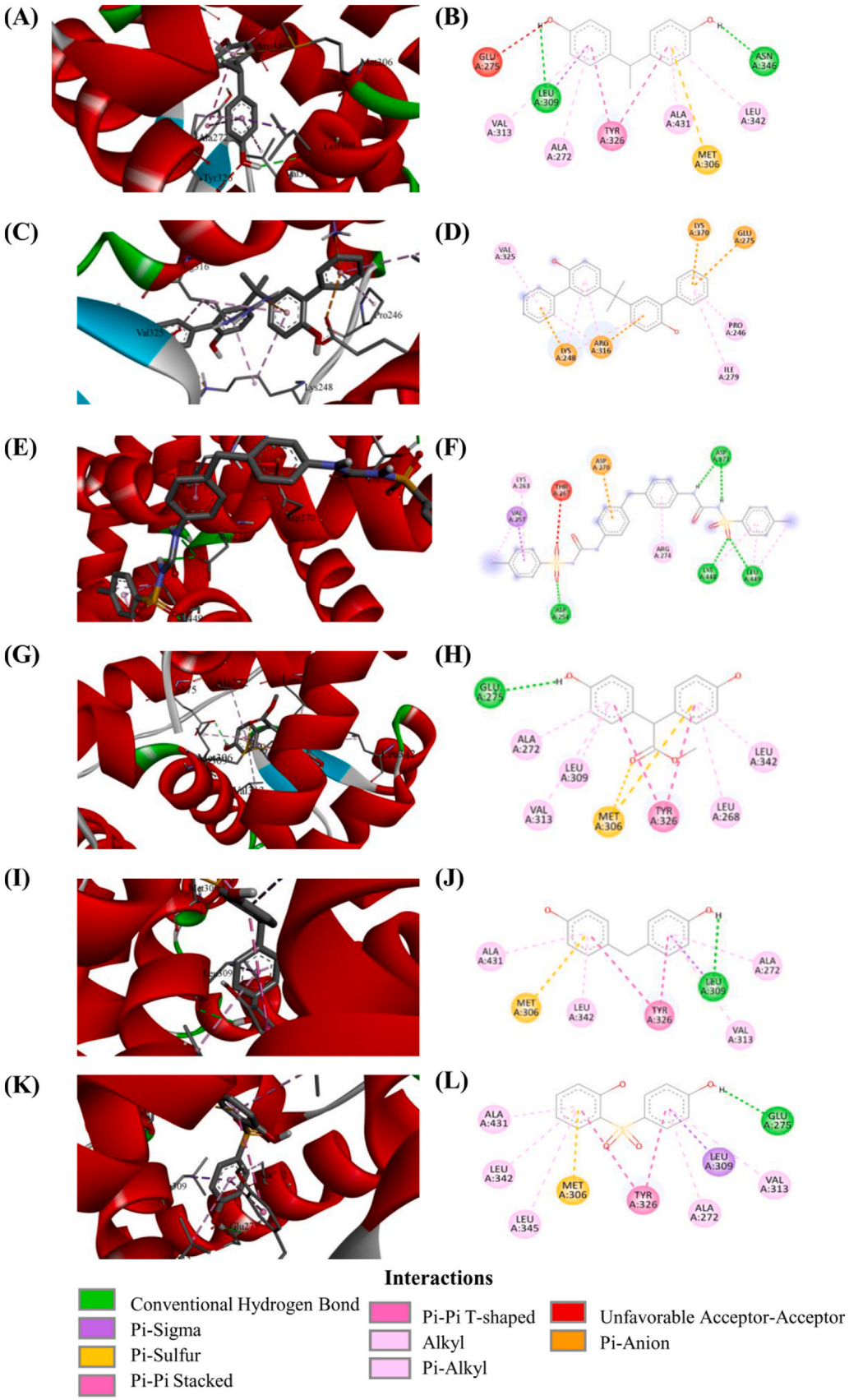

Fig. 2. 3D and 2D representations of binding interactions of the BPA compounds with ERRγ depicting key amino acid residues that contributed to the protein-ligand interactions **(A–B)** Bisphenol E, **(C–D)** Bisphenol PH, **(E–F)** BTUM, **(G–H)** MBHA, **(I–J)** Bisphenol F, **(K–L)** 2,4-BPS.

Table 2
Physicochemical properties and toxicity related information of estradiol and top ten BPA compounds sorted based on their binding free energy with ERRγ.

S. No.	BPA and its analogs	PubChem (CID)	Molecular Weight (g/mol)	LogP	H-bond donor	H-bond acceptor	Topological Polar Surface Area (Å^2)	Mutagenic	Tumorigenic	Irritant
1.	**Estradiol (reference)**	5757	272.4	4	2	2	40.5	No	No	No
2.	Bisphenol AF	73864	336.23	4.5	2	8	40.5	No	No	Yes
3.	Bisphenol Z	232446	268.3	5.4	2	2	40.5	No	No	Yes
4.	Bisphenol B	66166	242.31	3.9	2	2	40.5	Yes	Yes	Yes
5.	Bisphenol A	6623	228.29	3.3	2	2	40.5	No	No	Yes
6.	Bisphenol E	608116	214.26	3.9	2	3	40.5	No	No	Yes
7.	Bisphenol PH	13059052	380.5	7.3	2	2	40.5	No	No	Yes
8.	BTUM	3596056	592.7	6.1	4	6	167	Yes	Yes	No
9.	MBHA	78805	258.27	2.7	2	4	66.8	No	No	No
10.	Bisphenol F	12111	200.23	2.9	2	2	40.5	No	No	No
11.	2,4-BPS	79381	250.27	2	2	4	83	No	No	Yes

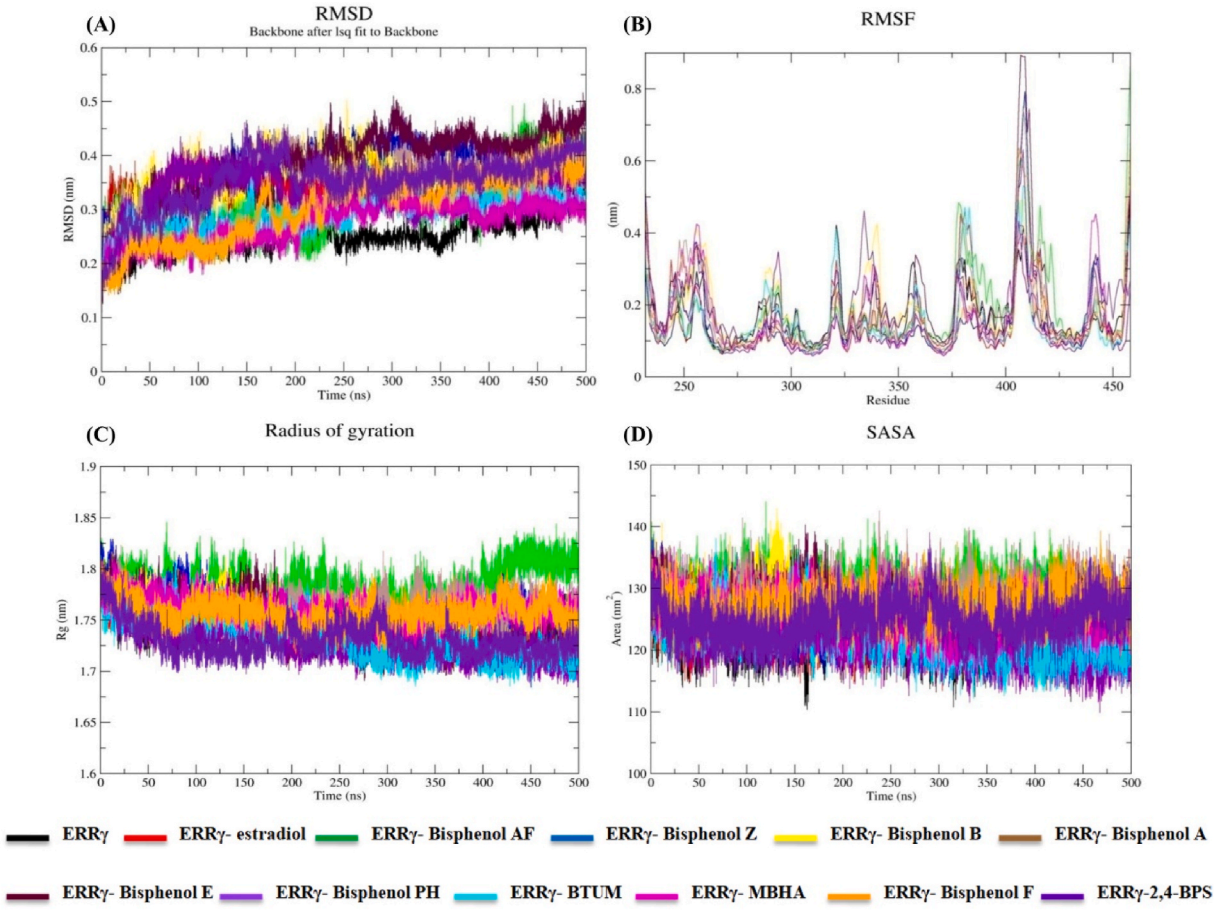

Fig. 3. Stability analysis (**A**) RMSD values for the ERRγ, ERRγ–estradiol and ERRγ–BPA compounds complexes. Flexibility analysis **(B)** RMSF values for the ERRγ, ERRγ–estradiol, and ERRγ–BPA compounds complexes.Compactness (**C**) Rg, and Solvent accessible surface area analysis (**D**) SASA values over 500 ns of simulations.

ERRγ–Bisphenol AF, ERRγ–Bisphenol Z, ERRγ–Bisphenol B, ERRγ–Bisphenol A, ERRγ–Bisphenol E, ERRγ–Bisphenol PH, ERRγ–BTUM, ERRγ–MBHA, ERRγ–Bisphenol F, and ERRγ–2,4-BPS complexes were calculated as 1.74, 1.78, 1.75, 1.75, 1.76, 1.74, 1.72, 1.73, 1.75, 1.75, and 1.72 nm, respectively (Fig. 3C).

3.4.4. SASA analysis

We used SASA analysis over a period of 500 ns of the simulation to determine how the ligand affected the solvent-accessible area. The average SASA values for the ERRγ, ERRγ–estradiol, ERRγ–Bisphenol AF, ERRγ–Bisphenol Z, ERRγ–Bisphenol B, ERRγ–Bisphenol A, ERRγ–Bisphenol E, ERRγ–Bisphenol PH, ERRγ–BTUM, ERRγ–MBHA, ERRγ–Bisphenol F, and ERRγ–2,4-BPS complexes were calculated as 122.10, 123.94, 129.02, 124.16, 126.44, 128.14, 125.87, 121.40, 123.00, 125.63, 127.07, and 124.60 nm^2. The SASA value of the ERRγ–Bisphenol AF complex was higher than that of ERRγ–estradiol and other complexes. A similar pattern was observed in all systems (Fig. 4D), indicating that comparatively few changes occurred after a compound was bound.

3.4.5. Interaction analysis

Hydrogen bonds (HBs) are an important bond for stabilizing protein–ligand interactions. Therefore, interaction analysis was conducted by means of hydrogen bonding over a time of 500 ns and plotted in Figs. 4 and 5. The reference ERRγ–estradiol complex exhibited 0–3 HBs. However, the number of HBs for ERRγ–Bisphenol AF, ERRγ–Bisphenol Z,

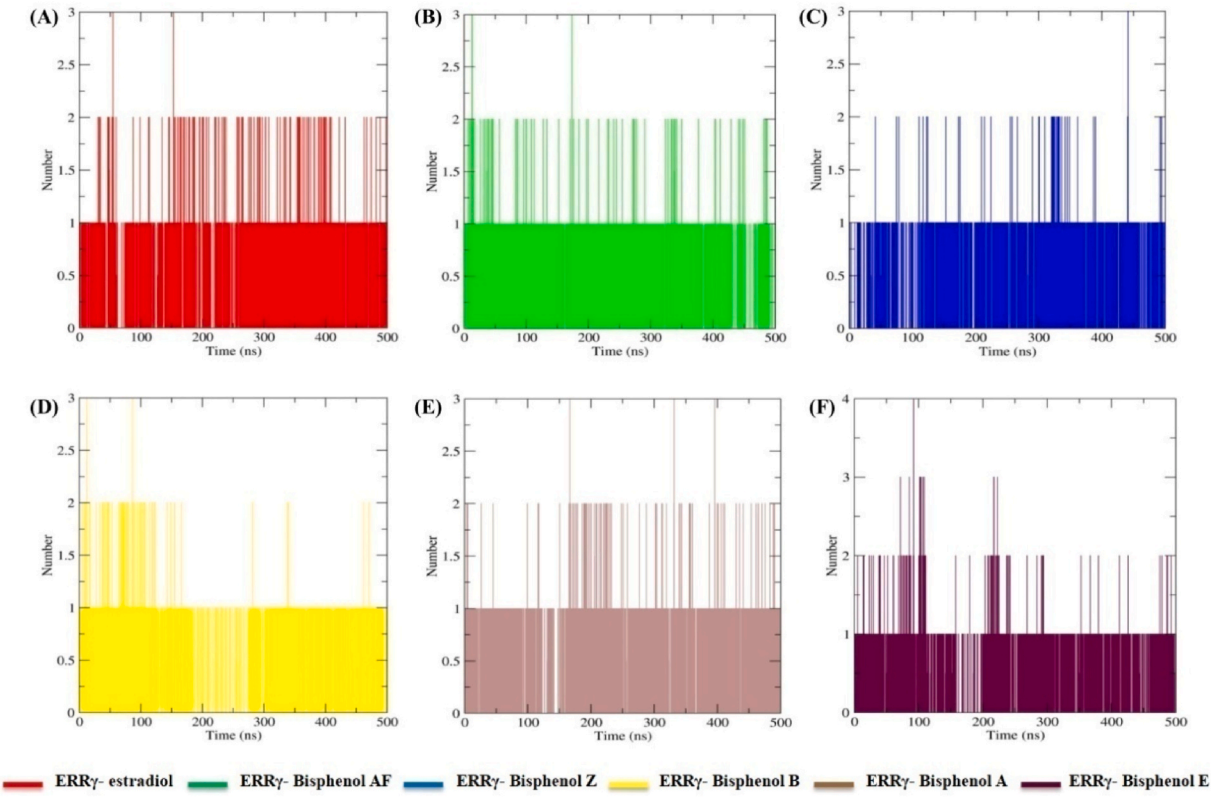

Fig. 4. Number of hydrogen bonds formed in each complex during the 500 ns of simulations. (A) Estradiol, (B) Bisphenol AF, (C) Bisphenol Z, (D) Bisphenol B, (E) Bisphenol A, and (F) Bisphenol E.

ERRγ–Bisphenol B, ERRγ–Bisphenol A, ERRγ–Bisphenol E, ERRγ–Bisphenol PH, ERRγ–BTUM, ERRγ–MBHA, ERRγ–Bisphenol F, and ERRγ–2,4-BPS were calculated as 0–3, 0–3, 0–3, 0–3, 0–4, 0–3, 0–5, 0–2, 0–3, and 0–5, respectively. Based on the analysis, BPA compounds showed similar HBs patterns with ERRγ as compared with reference estradiol. This suggests that the interactions between these BPA compounds and the ERRγ binding cavity are stable.

3.4.6. *Essential dynamic analysis*

In order to capture critical conformational changes during ligand binding, essential dynamics analysis was conducted using PCA. In general, the first few eigenvectors determine the overall motion of a protein. We therefore used the first 50 eigenvectors to analyze changes in structural movement. A clear understanding of the motions induced by ligand binding was achieved by calculating percentage-wise correlated motions from the initial five eigenvectors. ERRγ, ERRγ–estradiol, ERRγ–Bisphenol AF, ERRγ–Bisphenol Z, ERRγ–Bisphenol B, ERRγ–Bisphenol A, ERRγ–Bisphenol E, ERRγ–Bisphenol PH, ERRγ–BTUM, ERRγ–MBHA, ERRγ–Bisphenol F, and ERRγ-2,4-BPS showed 66.05%, 65.84%, 73.27%, 71.82%, 67.63%, 66.84%, 76.28%, 65.41%, 69.62%, 67.13%, 69.88%, and 68.92% correlated motions, respectively. Here, we can see that the ERRγ–estradiol and ERRγ–Bisphenol PH complexes showed the lowest motions (Fig. S1A). The first few eigenvectors of the protein are indicative of its overall dynamics. Thus, the first two eigenvectors were chosen and plotted in phase space. The ERRγ, ERRγ–estradiol, and ERRγ–Bisphenol PH clusters are most stable (low correlated motions) when compared to the others (Fig. S1B).

3.4.7. *Gibbs free energy landscape (FEL) analysis*

The first two principal components were used to calculate Gibbs free energy landscapes. The FEL for each system is illustrated in Fig. 6. In this diagram, blue represents the lowest energy conformational state (kcal/mol) and red represents the highest energy conformational state (kcal/mol). Energy values ranging from 0 to 17.2 kJ mol^{-1}, 0–17.4 kJ mol^{-1}, 0–17.6 kJ mol^{-1}, 0–18 kJ mol^{-1}, 0–17.3 kJ mol^{-1}, 0–17.5 kJ mol^{-1}, 0–20.5 kJ mol^{-1},0–17.9 kJ mol^{-1}, 0–19.6 kJ mol^{-1}, 0–17.6 kJ mol^{-1}, 0–18 kJ mol^{-1}, and 0–18.2 kJ mol^{-1} were observed for ERRγ, ERRγ–estradiol, ERRγ–Bisphenol AF, ERRγ–Bisphenol Z, ERRγ–Bisphenol B, ERRγ–Bisphenol A, ERRγ–Bisphenol E, ERRγ–Bisphenol PH, ERRγ–BTUM, ERRγ–MBHA, ERRγ–Bisphenol F, and ERRγ-2,4-BPS, respectively. All the systems have slightly different energies except for ERRγ, ERRγ–estradiol, ERRγ–Bisphenol AF, ERRγ–Bisphenol B, ERRγ–Bisphenol A, and ERRγ–MBHA complex, which have a slightly lower value. During simulation, these compounds followed the transitions that were energetically favorable.

3.4.8. *Binding free energy calculations and analysis of ERRγ amino acid residue contributing to the bindings*

To validate the binding affinities of the simulated complexes, MM-PBSA methods were used to estimate binding free energies. Our calculations were based on the final 10 ns of MD simulations. The calculated binding free energy for the ERRγ–estradiol, ERRγ–Bisphenol AF, ERRγ–Bisphenol Z, ERRγ–Bisphenol B, ERRγ–Bisphenol A, ERRγ–Bisphenol E, ERRγ–Bisphenol PH, ERRγ–BTUM, ERRγ–MBHA, ERRγ–Bisphenol F, and ERRγ–2,4-BPS complexes were −108.116, −177.045,−159.041, −179.361, −169.651, −161.610, −143.402, −117.713, −170.735, −158.911, and −138.332 kJ mol^{-1}, respectively. The calculated values of van der Waals, electrostatic, polar solvation, SASA, and binding free energies are presented in Table 3.

In order to determine which amino acid residues are crucial for ligand binding, residual binding energy analyses were performed on the simulated complexes. A significant interaction between BPA compounds and amino acid residues of ERRγ was observed, indicating the binding affinity of BPA compounds with respect to reference estradiol. Interactions were more influenced by amino acid residues from positions 240 to 280, 300 to 370, and 425 to 450 (Fig. S2).

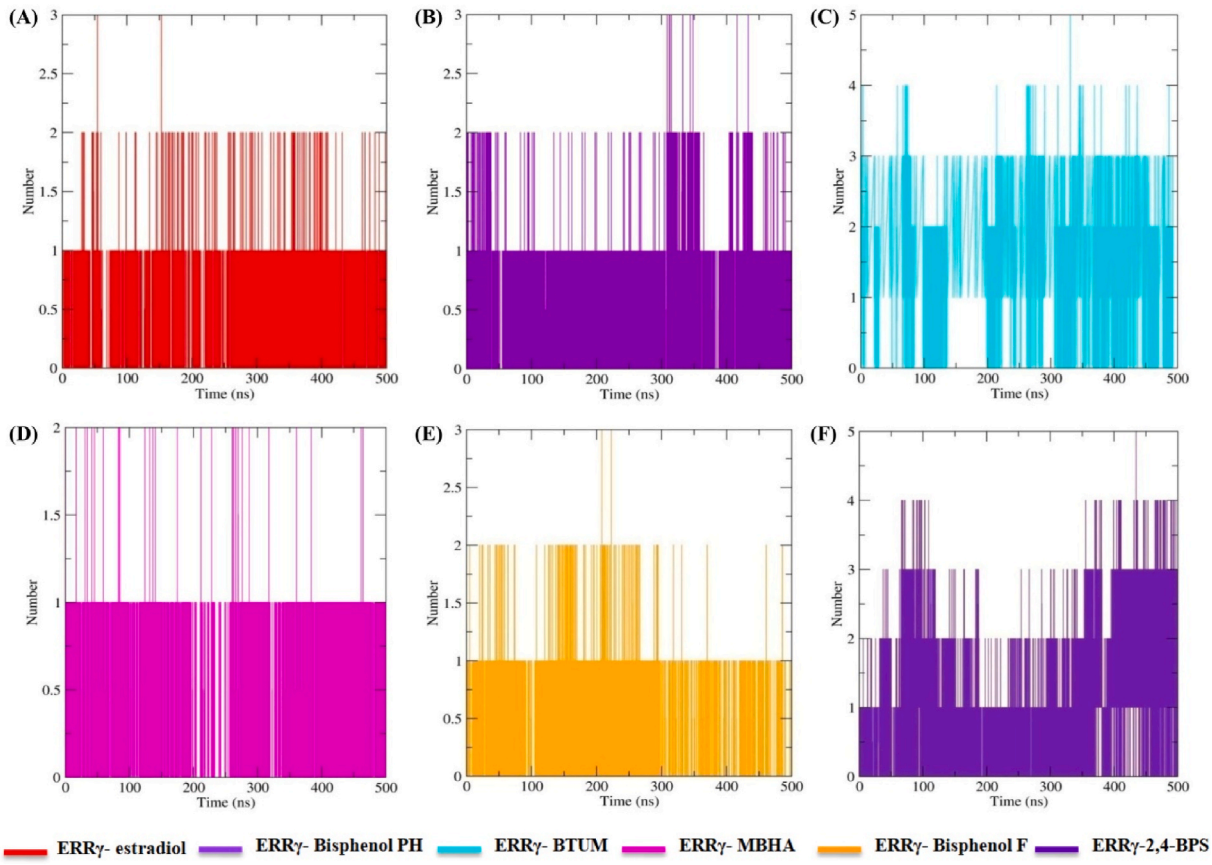

Fig. 5. Number of hydrogen bonds formed in each complex during the 500 ns of simulations. (A) Estradiol, (B) Bisphenol PH, (C) BTUM, (D) MBHA, (E) Bisphenol F, and (F) 2,4-BPS.

4. Discussion

There has long been evidence that BPA poses health risks and can adversely affect human health (Chouhan et al., 2014). There has been an increased focus on BPA over the last few decades owing to its widespread presence (Ye et al., 2009). There is also evidence that low levels of BPA have a biological effect, mimicking the effects of estrogen. Thus, BPA is categorized as an "endocrine disruptor" that can disrupt the body's chemical messenger system. Nonetheless, its chemical structure could offer an advantage, as evidenced by its ability to bind to the ER. In this context, BPA fails to fit properly within the hormone binding site; instead, it merely triggers a shift in the α-helices that make up the ligand binding domain (LBD) (Acconcia et al., 2015; Fonseca et al., 2022). A recent study indicates that exposure to BPA may influence the reactivity of human umbilical artery, leading to an elevation in the activity of L-type Ca2+ Channels (LTCC), a frequently observed vascular response in pregnancy-related hypertensive disorders. Therefore, exposure to BPA could be implicated in the emergence of pregnancy-related health issues (Fonseca et al., 2023). It is referred to as xenoestrogen because of its structural and functional similarities to estrogen, causing growing concern around the world because they can disrupt the development of children exposed to it in the womb (Chouhan et al., 2014). The decline of sperm counts and the increase in hormone-related cancers like breast, testicular, and prostate cancer may be linked to them. Several hormone-related effects, such as early puberty in girls, are associated with them, including birth defects of the reproductive tract (Castellini et al., 2020; Chouhan et al., 2014; Leonardi et al., 2017). Inadequate processing, marketing, and production of BPA materials regularly contribute to its exposure. Even the "BPA-free" label on these products is misleading, because they contain analogs of BPA (Rahman et al., 2021). The frequent use of BPA analogs in industries and their harmful effects on health and the environment have recently attracted global attention (Rahman et al., 2021). Therefore, efforts has been made in the present study to dissect the mechanisms and interacting features of BPA analogs with ERRγ to help develop therapeutics to minimize its harmful effects in future. Molecular docking was conducted to investigate interacting key amino acid residues of ERRγ. Molecular docking is a powerful computational approach to determining protein–ligand interaction, visualizing amino acid residues contributed to interactions via varied types of bonding, and investigate the best pose with minimum binding energy (Pathak et al., 2020; Singh and Pathak, 2021). Furthermore, physicochemical properties analysis and toxicity prediction, MD simulation, FEL, and binding energy calculations were performed. The binding energy of each BPA compound with respect to naturally occurring hormone estradiol was estimated.

By molecular docking, the nature of the interactions of BPA and its analogs with ERRγ with respect to reference estradiol were analyzed. After visualizing and analyzing protein–ligand interactions, the top ten BPA compounds and estradiol were subjected to physicochemical properties analysis and toxicity prediction, because it serves as an essential criteria to evaluate nature of candidate molecules computationally. Lipinski's rule of five is followed by BPA compounds, except for Bisphenol Z, Bisphenol PH, and BTUM. In order to satisfy Lipinski's rule, a molecule must have a molecular weight of less than 500 Da, a logP value of five, hydrogen bond donors of five, and hydrogen bond acceptors of ten (Lipinski et al., 2001). Based on pharmacokinetic predictions, these substances behave similarly to oral drugs and are readily absorbed by the bodies of humans and animals (Pires et al., 2015). Furthermore, the polar surface areas of BPA compounds indicates high permeability to the cell membrane (Prasanna and Doerksen, 2009). Mutagenic, tumorigenic, and irritant properties were also predicted in BPA compounds (Pathak et al., 2014; Pathak et al., 2020).

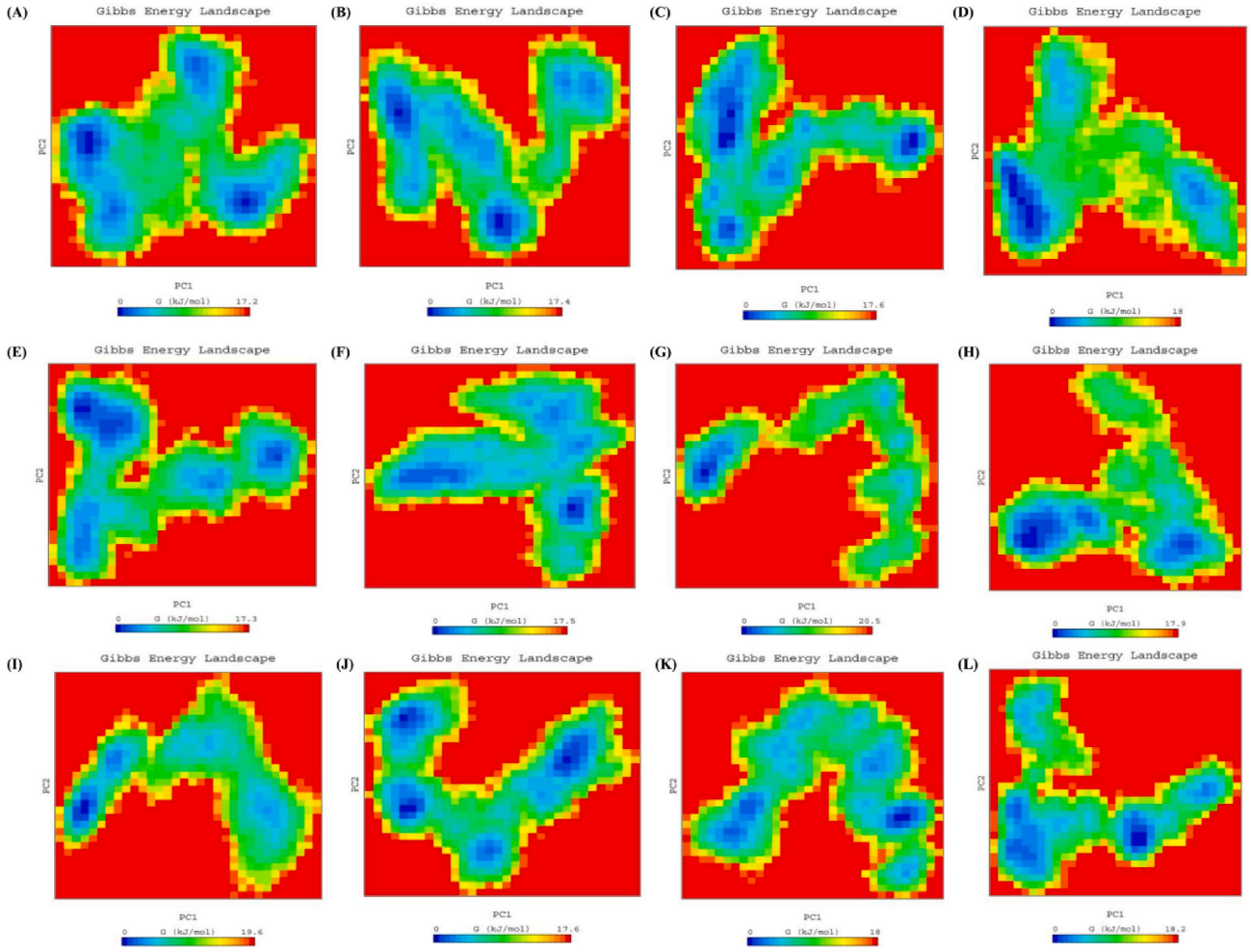

Fig. 6. Color-coded illustration of the Gibbs FEL was plotted using PC1 and PC2. The color bar indicates the Gibbs free energies (kcal/mol) for conformational states with the lowest (blue) and highest (red) energies. **(A)** ERRγ,**(B)** ERRγ–estradiol, **(C)** ERRγ–Bisphenol AF, **(D)** ERRγ–Bisphenol Z, **(E)** ERRγ–Bisphenol B, **(F)** ERRγ–Bisphenol A, **(G)** ERRγ–Bisphenol E, **(H)** ERRγ–Bisphenol PH, **(I)** ERRγ–BTUM, **(J)** ERRγ–MBHA, **(K)** ERRγ–Bisphenol F, and **(L)** ERRγ–2,4-BPS complex. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Binding energy of BPA and its analogs with Human ERRγ (van der Waals and electrostatic forces, polar solvation, SASA, and binding free energy in kJ mol^{-1}).

S.N.	BPA and its analogs	van der Waals energy	Electrostatic energy	Polar solvation energy	SASA energy	Binding energy
1.	Estradiol	−127.031 ± 10.003	−3.893 ± 3.054	36.662 ± 11.388	−13.854 ± 1.239	−108.116 ± 9.197
2.	Bisphenol AF	−181.034 ± 8.213	2.676 ± 2.398	18.097 ± 4.301	−16.784 ± 0.761	−177.045 ± 8.464
3.	Bisphenol Z	−166.777 ± 9.037	−0.486 ± 2.153	24.850 ± 7.394	−16.629 ± 0.924	−159.041 ± 10.072
4.	Bisphenol B	−181.081 ± 8.045	−0.524 ± 1.612	18.352 ± 3.093	−16.109 ± 0.782	−179.361 ± 8.040
5.	Bisphenol A	−173.885 ± 7.500	1.385 ± 1.372	17.846 ± 5.089	−14.997 ± 0.764	−169.651 ± 8.141
6.	Bisphenol E	−164.106 ± 7.046	3.431 ± 1.197	13.557 ± 3.654	−14.492 ± 0.791	−161.610 ± 7.732
7.	Bisphenol PH	−201.134 ± 11.978	1.232 ± 2.432	75.765 ± 18.715	−19.265 ± 1.096	−143.402 ± 18.025
8.	BTUM	−230.787 ± 15.916	−65.040 ± 15.445	199.614 ± 27.644	−21.499 ± 1.383	−117.713 ± 18.925
9.	MBHA	−185.446 ± 8.091	0.239 ± 1.900	30.960 ± 6.289	−16.487 ± 0.763	−170.735 ± 9.383
10.	Bisphenol F	−160.069 ± 7.611	−0.451 ± 0.856	15.734 ± 2.464	−14.126 ± 0.770	−158.911 ± 7.655
11.	2,4-BPS	−170.861 ± 10.834	−31.071 ± 6.462	78.661 ± 7.244	−15.061 ± 0.777	−138.332 ± 10.872

We performed MD simulations to assess the stability of each BPA compound–ERRγ complex and compared it with the estradiol–ERRγ complex. This method can be used to predict how macromolecules will behave before and after they bind to ligands (Abraham et al., 2015). We then calculated the binding free energy of the top ten BPA compounds over time, followed by an analysis of the contribution of each amino acid residue in ERRγ, which is involved in the interactions. RMSD analysis indicated that all systems stabilized over 500 ns, suggesting that the BPA compounds interact notably with the ERRγ. By analyzing 500-ns trajectories, other parameters, such as RMSF, Rg, SASA, H-bonds, PCA, and FEL, were determined. The results of the analysis suggest that the binding of BPA compounds changes both the conformation of the ERRγ and the dynamics needed to interfere its normal activity.

MM-PBSA binding free energy and residual binding energy calculations were used to further analyze the BPA compounds' binding affinity towards the ERRγ. Based on MD simulation results, this method calculates the binding free energy of protein–ligand complexes (Kumari et al., 2014). The strength of the association between each BPA compound and ERRγ was determined by measuring binding energy. A negative value indicated a strong affinity. It follows that lowering the binding energy

enhances the interactions, and that high binding affinity is related to lower binding energies for protein–ligand complexes (Wan et al., 2020). Based on our analysis, the BPA compounds showed more binding affinity with ERRγ as compared to estradiol (Babu et al., 2012; Ohore and Zhang, 2019). During the calculation of binding energy using MM-PBSA, Bisphenol B was predicted to bind to ERRγ with a higher affinity compared to other selected compounds. Analysis of the protein-ligand complex obtained from molecular docking revealed that it forms two conventional hydrogen bonds with ERRγ Glu275 and Asn346. However, it was also predicted to be mutagenic, tumorigenic, and irritant. Similar results were obtained for the binding affinity of other BPA analogs, with slight differences in binding energy. These findings were further supported by additional analyses conducted in the present study. Therefore, all BPA analogs included in this study are considered to be potentially dangerous for human health and should be prioritized for further investigation (Babu et al., 2012; Vorkamp et al., 2021). This study, therefore, contributes to understanding the estrogenic activity by providing information about possible structure–activity relationships and development of possible therapeutics by antagonizing bisphenols-ERRγ interactions.

5. Conclusion

In general, humans are exposed to BPA and its analogs every day. Prolonged BPA exposure is very injurious to health as it is endocrine disruptor. In our daily lives, we use many products that contain BPA or its analogs, but the potential toxic effects have become a hot topic for research within the scientific community. The present study utilized a number of computational methods to investigate the mechanisms and interacting features of BPA and its analogs with human ERRγ with respect to naturally synthesized hormone estradiol. The study indicate that the binding affinity of BPA and its analogs with ERRγ were higher than estradiol, providing its physicochemical and toxicity related information as well as identifying key amino acid residues of ERRγ contributing to the binding. The study provides a roadmap for understanding the structure–activity relationships and estrogenic activity of BPA compounds. Furthermore, the interacting amino acid residues of ERRγ can be utilized to antagonize bisphenols-ERRγ interactions for future therapeutics, mitigating their toxicity.

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CRediT authorship contribution statement

Rajesh Kumar Pathak: Conceptualization, Methodology, Software, Visualization, Formal analysis, Investigation, Writing – original draft. **Jun-Mo Kim:** Conceptualization, Resources, Supervision, Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.123549.

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