Proceedings of the 3rd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/98/2025.21471

Investigation of the Interaction between Triphenyl Phosphate and Endocrine Nuclear Receptors: A Molecular Docking-Based Analysis

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Abstract: The class of endocrine-disrupting pollutants within the realm of emerging contaminants has been increasingly subjected to intense scrutiny as a result of their presumed potential to imperil human health. Nevertheless, the interaction of triphenyl phosphate (TPP), a flame retardant, with endocrine nuclear receptors has received relatively less research attention, yet it has nevertheless managed to capture international notice. In a forthcoming event, the European Chemicals Agency (ECHA) has announced its intention to incorporate triphenyl phosphate into the list of Substances of Very High Concern (SVHC) in the early days of November 2024. In this study, the binding of TPP to the estrogen receptor (ER), androgen receptor (AR), and progesterone receptor (PR) was explored through the utilization of a molecular docking approach with the assistance of AutoDockTools software. The results demonstrated that TPP was indeed able to dock successfully with ER, AR, and PR. Notably, the binding affinity of TPP to PR was the most pronounced, exhibiting a binding energy of -8.01 kcal/mol, thereby suggesting that TPP has the potential to disrupt the endocrine system by interacting with multiple nuclear receptors. From a molecular perspective, TPP might function as a broad-spectrum endocrine disruptor. This provides a foundation for further investigation into its endocrine-disrupting mechanisms and underscores the need for a more comprehensive assessment of its environmental and health ramifications.

Keywords: Triphenyl phosphate, Molecular docking, Nuclear hormone, Endocrine disrupter, Emerging Contaminants

1. Introduction

Emerging contaminants (ECs) are newly discovered chemical substances or biological agents found in the environment, which can be hazardous to humans and ecosystems. They are considered to be potentially hazardous to humans and ecosystems [1]. Contaminants of emerging concern (CECs), particularly in aquatic ecosystems, can negatively impact both ecosystems and human health, even at low concentrations [2]. Emerging contaminants can be classified into four broad categories: persistent organic pollutants (POPs), endocrine disruptors, microplastics, and antibiotics. Endocrine disruptors interfere with hormonal signaling pathways and pose risks to reproductive health, development, and metabolism. Organophosphate esters (OPEs) are an emerging class of environmental pollutants, with

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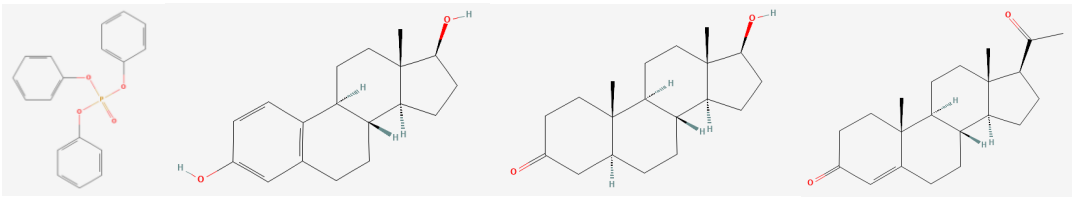
applications in flame retardants and plasticizers [3]. China is the primary producer and consumer of OPEs, with Triphenyl phosphate (TPP) being one such chemical [4]. Triphenyl phosphate (TPP) is one such chemical and is employed extensively as a flame retardant in numerous industrial contexts, including the manufacture of plastics, electronics and furniture [5]. However, its widespread use has raised concerns about its environmental and human health impacts, particularly in light of evidence suggesting its potential to disrupt endocrine function. This study examines TPP as a potential endocrine disruptor using molecular docking techniques. Molecular docking is a computational simulation technique to predict the binding pattern and affinity between ligands and receptors, which can rapidly predict and screen a large number of endocrine disruptors that bind to receptors. This significantly improves efficiency and reduces research costs. [6]. [7]. The study uses AutoDockTools software to perform molecular docking of triphenyl phosphate and three endocrine nuclear receptors, using endogenous endocrine hormones as positive controls.

2. Material and method

2.1. Ligand Molecules Preparation

The ligand molecule selected for docking in this study was triphenyl phosphate, and estradiol, dihydrotestosterone, and progesterone were used as the control ligand molecules for docking estrogen receptor, androgen receptor, and progesterone receptor, respectively. The chemical abstract numbers were 115-86-6, 50-28-2, 521-18-6, and 57-83-0, and the relative molecular masses were 326.28, 272.4, 290.44, and 314.46 g/mol. The molecular structures are shown in Figure 1. The molecular conformations of the ligand molecules were obtained from the PubChem database and exported in SDF format. The Open Babel software was used to convert the conformations to the target conformations of the ligand molecules required for docking, and then they were converted to PDB format and imported into AutoDockTools 1.5.6 software for preprocessing, hydrogenation, and rotation of ligands for docking, and then the conformations were saved in the format of PDBQT, which was used for further molecular docking studies.



Triphenyl phosphate Estradiol Dihydrotestosterone Progesterone

Figure 1: Molecular structure of ligand

2.2. Receptor Molecules Preparation

The amino acid sequences of the receptor molecules ERα (6V8T), ERβ (1L2J), AR (1T63), and PR (1E3K) proteins were queried on the website of the National Center for Biological Information and were screened and compared with the Protein Structure Database to obtain their 3D conformations. The conformations were displayed in PyMOL software, and the redundant chains, water molecules, and small molecules were removed from the conformations, and the conformations were saved in PDB format. The hydrotreatments were performed by AutoDockTools software and saved as PDBQT files for further molecular docking studies.

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2.3. Molecular Docking

The initial step involves importing the receptor proteins and small molecules into AutoDock. The Grid Box module is then utilized to select all potential docking sites, with the docking box size, coordinates, number of grid points, and distance between grid points being set accordingly. After the regions have been selected, they are saved in GPF format, and the autogrid module should be run. After the regions have been selected, they are saved in GPF format, and the autogrid module is executed. Subsequently, the parameters and calculation method for AutoDock are prepared, and semi-flexible docking is selected. The number of dockings is set to 10, and the values of the maximum number of evaluations and the maximum number of generations are optimized. Next, the docking parameters must be set and exported in DPF format for calculation. This process generates a file in DLG format, which is subsequently analyzed to determine the docking results. The optimal result is determined as the one with the highest absolute value of binding energy and hydrogen bonding. Finally, the molecular file of the optimal result is saved in PDBQT format. This file is also converted to PDB format using Open Babel software and employed to visualize the docking results in PyMOL.

3. Result and discussion

3.1. Docking results

3.1.1. Docking results of triphenyl phosphate with 2 ERs

The ligand triphenyl phosphate interacts with the key residue SER-512 of ERα through hydrogen bonding, with hydrogen bonding distances of 2.7 Å and 3.3 Å, respectively (Figure 2), indicating a relatively tight binding. In addition, the spatial conformation of the receptor binding site provides structural support for the stable binding of the ligand. These results provide an intuitive basis for the study of the mechanism of action of triphenyl phosphate with ERα and provide guidance for subsequent drug design.

Triphenyl phosphate forms an interaction with GLY-318, a key residue of ERβ, via a hydrogen bond with a hydrogen bond distance of 2.1 Å (Figure 3).

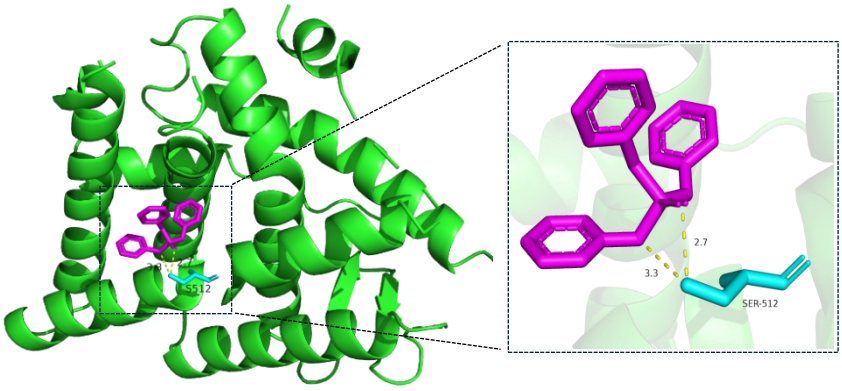

Figure 2: Three-dimensional conformation of triphenyl phosphat e binding to ERα

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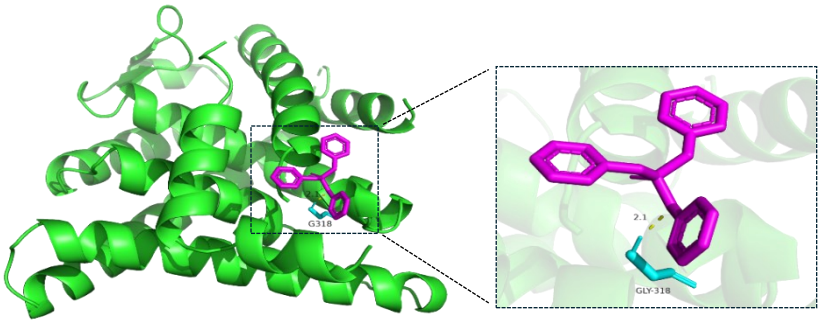

Figure 3: Three-dimensional conformation of triphenyl phosphate binding to ERβ

3.1.2. Docking results of triphenyl phosphate with AR

The triphenyl phosphate molecule interacts with ARG-752, a key residue of the androgen receptor AR, via two hydrogen bonds with distances of 2.0 Å and 2.4 Å, respectively (Figure 4).

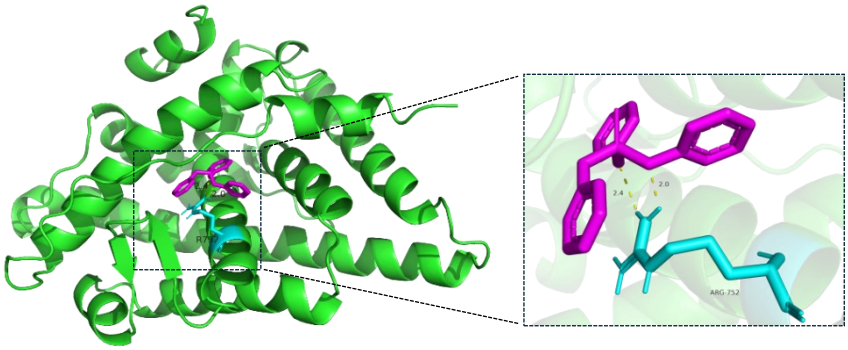

Figure 4: Three-dimensional conformation of triphenyl phosphate binding to AR

3.1.3. Docking results of triphenyl phosphate with PR

The interaction between triphenyl phosphate and the key residue SER-728 of the progesterone receptor PR is facilitated by a hydrogen bond with a hydrogen bond distance of 1.9 Å (Figure 5).

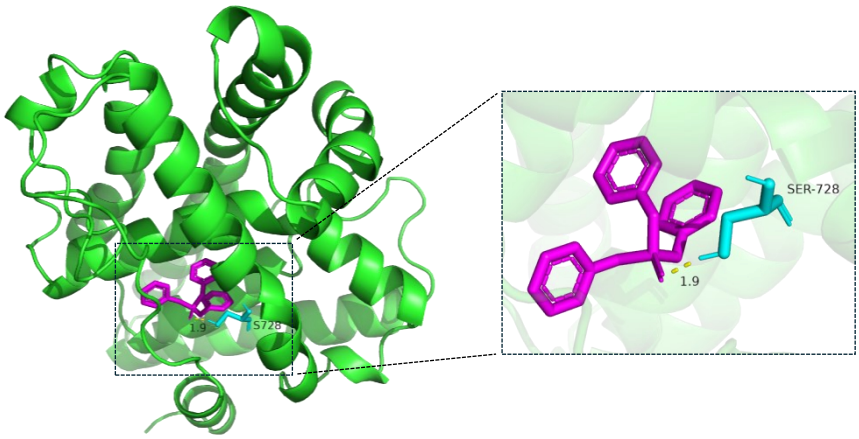

Figure 5: Three-dimensional conformation of triphenyl phosphate binding to PR

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3.2. Comprehensive comparison of docking results

Table 1 presents the binding affinity, number of hydrogen bonds versus number of linked residues, for all compounds obtained by molecular docking. The findings suggest that TPP can successfully dock with all three endocrine nuclear receptors, with the highest binding affinity for progesterone (PR). TPP exhibits a lower affinity for binding to endocrine nuclear receptors in organisms compared to other endogenous ligands. However, prolonged exposure or high concentrations may potentially disrupt the endocrine system. The substance may affect the signaling pathways of hormones involved by mimicking the structure of endogenous hormones and binding to these receptors. In order to illustrate the mechanism of action of the TPP, Figure 6 presents an example based on the estrogen receptor. The potential for TPP to compete with endogenous hormones for receptor binding sites could result in disruption to hormone levels or abnormal signalling. TPP has been observed to exert a multi-receptor effect and act as a broad-spectrum endocrine disruptor.This study is based on theoretical simulations and requires further validation through experimental studies, such as in vitro receptor binding assays and cell function experiments, to provide a more comprehensive and accurate basis for assessing the risk of endocrine disruption by TPP.

Table 1: Molecular docking information of 4 ligand molecules with 4 receptor proteins

Molecules	Binding energy (kcal/mol)	Number of hydrogen bonds	Number of linked amino acid residues
E2			
ERα	-9.39	3	3
ERβ	-9.17	3	3
TPP			
ERα	-5.79	2	1
ERβ	-4.91	1	1
DHT			
AR	-11.11	3	3
TPP			
AR	-7.92	2	1
P4			
PR	-10.91	3	2
TPP			
PR	-8.01	1	1

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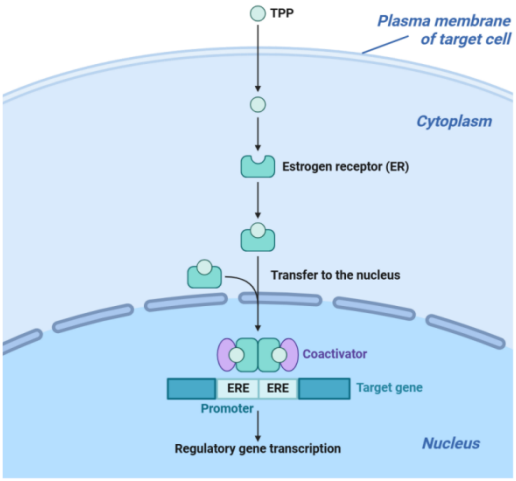

Figure 6: Mechanism of TPP and estrogen receptor action

3.3. Correlation analysis of theoretical simulations with known experimental results

A number of experimental studies have demonstrated that triphenyl phosphate can exert an effect on endocrine nuclear receptors, thereby causing adverse health effects in animals and humans. The study by Kwon et al. showed that TPP exposure affects cell cycle progression in human Ishikawa endometrial cancer cells by altering the expression of estrogen and progesterone receptors through experiments on Ishikawa cells [8]. In zebrafish experiments, exposure to TPP resulted in a reduction in the levels of reproductive hormones, which in turn impeded the DNA damage repair system in zebrafish hepatocytes [9]. Additionally, TPP exposure has been demonstrated to impact the reproductive capacity of Cryptomeria japonica, resulting in an increase in the number of apoptotic gonadal cells and a reduction in the number of developing embryos within the uterus [10]. Liu et al. showed a significant correlation between TPP and 2-ethylhexyl diphenyl phosphate (EHDPP) and the risk of breast and cervical cancer by means of plasma sample analysis [11]. With the ability to disrupt hormonal pathways, TPP has also been shown to act as an agonist or antagonist of the AR [12]. In conclusion, the results of the molecular docking presented in this paper are in accordance with the findings of existing experimental studies.

4. Conclusion

Triphenyl phosphate (TPP) has been found to be a broad-spectrum endocrine disruptor, interacting with multiple nuclear hormone receptors. Molecular docking showed that TPP can successfully dock with estrogen, androgen and progesterone receptors, and the binding with PR is strongest. This broad-spectrum activity raises concerns about its cumulative and long-term effects on the endocrine system, potentially disrupting reproductive health, development, and metabolism. TPP has been associated with endocrine disruption in various biological models, and its effects on hormone levels, receptor expression, and reproductive outcomes are evident in both in vitro and in vivo systems. Further experimental validation is needed to understand the mechanism of TPP's endocrine-disrupting effects. Future studies should focus on in vitro receptor binding assays, cell-based functional analyses, and in vivo toxicity studies to assess TPP's endocrine-disrupting properties.

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