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Review Article

Application of Molecular Docking Methods on Endocrine Disrupting Chemicals: A Review

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Abstract

Endocrine-disrupting chemicals (EDCs) interfere with hormone receptors and are associated with a variety of adverse health effects. Therefore, there is a rising global concern about these substances. Numerous xenobiotic substances released into the environment are classified into EDCs that adversely affect the developmental and reproductive functions of living species. The mode of the action of these substances are directly or indirectly binding to the hormone receptors and abnormally controls the hormonal activity. However, major challenges exist in order to analyse the effect of these substances experimentally as it is associated with experimental costs and performance time. Therefore, the bioinformatics basis of the study is used as an alternative to experimental approaches by many researchers. Popular computational methods such as molecular docking is currently used to predict the effect of the EDCs on the endocrine receptor. Molecular docking method uses the EDCs as ligand and hormonal receptor proteins as the target and computationally evaluates the binding affinity, conformational changes and stability. Also, this is the ultimate leads to understand the structural and functional aspects. In this review, specifically the bioinformatics resources and implementation of molecular docking methods towards the evaluation of toxicity, binding affinity, classification of the potential endocrine disrupting substances have been discussed by narrating the literature.

Keywords: Bioinformatics, Endocrine-Disrupting Chemicals, Computational Tools, Molecular Docking, Hormone Receptor, Metabolic Pathway Analysis

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Introduction

Endocrine disruptors are widely dispersed in the environment, belong to the harmful chemical substances that interfere with the endocrine system and cause adverse physiological (developmental, reproductive, and neurological) effects on humans and other wildlife. Various categories of substances such as pharmaceuticals, dioxin, and dioxin-like compounds (DLCs), halogenated compounds like PCBs also belong to the potential endocrine disruptors.[1,2] In addition, the substances which are found in plastic bottles, detergents, flame retardants, food, toys and cosmetics also belong to this group.[3] Many pesticides such as DDT and azole have been identified as endocrine-disrupting chemicals (EDCs) due to their ability to bind sex-steroid hormone receptors.[4] These EDCs and also possesses of bio-accumulation and persistent properties are responsible for reproductive problems such as reduced fertility, male and female reproductive tract abnormalities, loss of foetus, changes in hormone levels; early puberty, impaired immune functions, several types cancers and so on.[5]

Animal studies have shown the impact and activity of the endocrine disruptors that influence the endocrine system and cause the alternation in the normal hormonal functions (Figure 1).

Some of the basic mechanisms have been described in literature and are presented in the below section.[4,6]

- The EDCs can completely mimic the naturally occurring hormones in the body like estrogens (the female sex hormone), androgens (the male sex hormone), and thyroid hormones.
- Sometimes, these substances bind to a receptor within a cell and disrupt the action of the endogenous hormone from binding, so fails to occur without responding properly.
- Also, the EDCs interferes with the natural hormones and their receptors cause the alternation in their normal metabolism.

Bioinformatics Application on Endocrine Disruptor Chemicals

Many of the known chemicals exhibit the endocrine disruptor activity, but their exact mode of action of these substances on the metabolism is still unknown.[7] The experimental screening process of these endocrine disruptor molecules involves animal-based toxicity screening, and testing, are time-consuming as well as cost-intensive processes.[8] Therefore, it is important to implement the computer-based application to

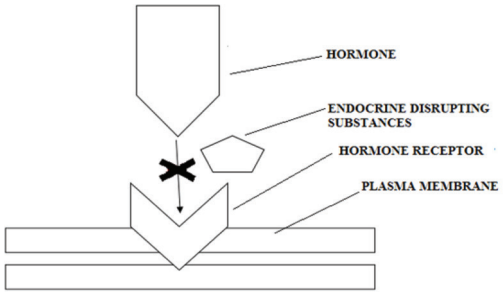

Figure 1. The Mechanism by Which the Endocrine Disrupting Chemicals Interfere with the Membrane Receptor Thereby Blocking the Signal System.

analyse the endocrine disruption effect at the molecular level. The basic objective of bioinformatics (computer application on the molecular data) rely on effective storing, processing and analysing the biological information by using the database and analytical tools. In this context, the implementation of bioinformatics-based tools and techniques can be used to frame the relationship between the compound and its toxic effect.[9,10] A key prerequisite for successful application of computational modelling technique is relay on the availability of three-dimensional (3D) structure of biomolecules in the database. By choosing an appropriate 3D structure of the biomolecule (ligand and receptor) in the molecular modelling research, it is possible to analyse the accuracy and scientific nature of the model.[11,12]

A wide number of web bioinformatics-based applications (tools) specifically for the analysis of EDCs are available in the literature (Table 1). However, the most popular computational techniques used specifically for the prediction and analysis of binding of EDCs to its receptor is the *molecular docking* approach, described below.

Molecular Docking Principles and Methods

Molecular docking is a method that predicts the proper orientation of one molecule (ligand) to a second molecule (receptor) when bound to each other to form a stable complex by using an automated computer algorithm (Figure 2). The process computes three basic features such as the *orientation* of the compound (ligand) concerning to the receptor, *conformational geometry*, and the *score* in terms of binding energy and free energy.[13,14] While performing a docking study, the *searching* and *scoring algorithms* must be chosen carefully so that, it should be validated for that particular protein-ligand system.[15]

Most commonly, the docking programs utilize several search algorithms while executing the program. Such algorithms which are widely used are Genetic algorithm, fragment-based search algorithms, Monte Carlo simulations and molecular dynamics approaches. Similarly, different scoring functions are also used to differentiate between actual binding processes between the receptor and ligand from all the other processes. Basically, three major categories of scoring functions are used: *force field*-based (computes binding energy by evaluating the van der Waals and electrostatic force of interaction between the atoms of protein-ligand complex), *empirical*-based (estimate the binding affinity of a protein-ligand complex by summing up energy associated with hydrogen bonds, hydrophobic interaction, steric clashes of atoms etc) and the *knowledge*-based (that obtain the pairwise potentials from available 3D structures of a large set of protein-ligand

Table 1. Computational Resources Available for Analysis of Endocrine Disruptor Chemicals

Tools/Database	Availability	Application
TiPED	http://www.tipedinfo.com	Applicable for the design and synthesis of safer molecules avoiding EDCs like chemicals
ToxCast	https://actor.epa.gov/dashboard	An interactive tool for use of chemical screening data from the toxicity generated by EDC
Endocrine Disruptome	http://endocrinedisruptome.ki.si/prediction.html	Prediction of structural aspects of endocrine action
Endocrine Disruptor Knowledge Base (EDKB)	http://edkb.fda.gov/webstart/edkb/index.html	Computational prediction of toxicology models.
Virtual tox lab	http://www.biograf.ch/index.php?id=projects&subid=virtualtoxlab	Prediction of the toxic potential of endocrine and metabolic disruption,
EDCs DataBank	http://edcs.unicartagena.edu.co	A database of endocrine disrupting chemicals (EDCs) with available three-dimensional structures
Pesticide Information Profiles (PIPs)	http://extoxnet.orst.edu/pips/ghindex.html	Database of pesticides contains information about endocrine disruptor properties
Endocrine active substances information (EASIS)	https://ec.europa.eu/jrc/en/scientific-tool/endocrine-active-substances-information-system-easis	Used to search for results from scientific studies on chemicals related to endocrine activity.
Environmental Bioinformatics Knowledge Base (ebKB)	http://ebkb.org/	Evaluation, organization of information based on analysis of environmental and biological systems and of their interactions
Database of Endocrine Disrupting Chemicals and their Toxicity profiles (DEDuCT)	https://cb.imsc.res.in/deduct/	Two-dimensional (2D) and three-dimensional (3D) chemical structure of 686 EDCs
NureXbase	http://www.nursa.org	Information on chemical structure, crystal structure, physical descriptors, nuclear receptors and mechanism of endocrine action

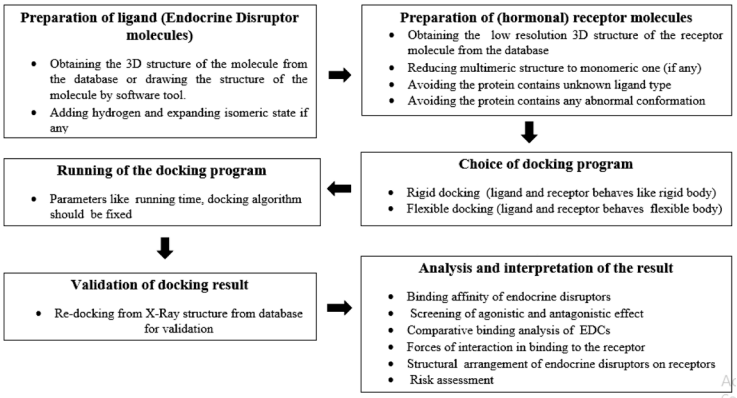

Figure 2. Computational Molecular Docking Methods Involving Hormone Receptor and Endocrine Disruptors and the Prediction Details.

complexes). Usually, there are 3 types of docking programs are available based on the flexibility/ rigidity consideration of receptors or ligands while performing the docking simulation. These are flexible ligand docking (receptor is rigid and ligand is flexible), rigid body docking (both ligand and receptors behave as rigid molecules) and flexible docking (in which both ligand and receptor molecules behave as flexible). In the docking simulation, one of the important aspects is charge addition to the ligands. This is done by adding or removing hydrogen atoms because in the physiological condition the ligand molecules are not neutral. Similarly, in the case of receptor preparation, presence of water molecules in the crystal structure of the receptor are to be optimized to avoid unnecessary interference in the active site.[16-18]

Analysis of Endocrine Disruptor Molecules by Molecular Docking Method

Currently, this method is widely used to predict the quantitative and qualitative mode of interaction between EDCs with its hormone receptor protein.[19,20] Celik et al presented a comparative docking study for the known representative class of hER alpha ligands along with small organic compounds like PCBs, plasticizers, and pesticide molecules for assessing the activity on nuclear receptors. In this work, the docking study was used to find out the variable conformations of the ligand in the ligand-binding domain (LBD) of the receptor. The agonistic protein structure (hER alpha) was selected from the PDB (PDB ID: 1A52, 1GWR) and for antagonistic structure, PDB ID 3RT was selected. Ligand molecules were designed *in silico* by using the Maestro program and subsequently, energy minimized. Finally, docking was performed by GLIDE 4.0 tool. Most of the EDC molecules were observed to bind in the steroid-binding cavity of the receptor, by the help of two hydrophilic ends and the hydroxylation of aromatic compounds was observed to increase in the binding affinity.[21] Similarly, the study about the interaction of the compounds with the estrogen receptor (ER) has been evaluated by the docking method. The effect of these compounds on a variety of metabolic functions and progression of the disease such as regulation of immune activity, appropriate brain function, and fetal development is discussed by Ng et al.[22] Experimental mode of binding study of Bisphenol A with the thyroid hormone receptors was conducted by Moriyama et al in 2002. The study revealed that the bisphenol A (BPA) molecule antagonistically binds to the thyroid receptor and disrupts the thyroid hormone action by suppressing its transcriptional activity measured.[23] A novel screening method was implemented to screen the potential endocrine-disrupting chemicals as *agonist* or *antagonist* based on in-silico docking study (agonistics/antagonistic differential docking method) by using Autodock 3 Tool. The target molecules in this case were taken from the available three-dimensional structure of human ER in PDB (PDB ID: 1ERE, 3ERD, 1 ERR and 3ERD). In this work, in the LBD alternation in the conformation of the ligand occurs that depends upon the binding of the molecules was obtained. The docking result was then compared to the crystallographic structures of both agonist/antagonist bound LBDs for further discrimination of the binding pattern. The docking result was further supported by *in vitro* estrogen binding receptor assay and luciferase gene reporter assay suggests that the ligand 4-(1 Admantyl Phenol) is a potential endocrine-disrupting chemical.[24] Several docking simulations between various EDCs molecules and their receptors have been performed by many researchers to quantify the adverse effect of these substances and some of the popular docking program and their availability is mentioned in Table 2.

The docking study of the small designed molecules with ER alpha (hERalpha) by Sun et al revealed that these compounds having potential to replace the natural ligand (hormone) and inhibit the activity. It was observed that 4 hydrophobic residues within the nuclear receptor box sequence are important for binding of the ligands. Also, the study was confirmed by the *in vitro* binding analysis between chemically synthesised ligand molecules with the receptor by reporter gene assay method.[25] In another study, molecular docking method was performed to figure out the anti-estrogenic properties of polybrominated diphenyl ethers (PBDE) compounds as human estrogen receptor alpha (hER-α) and antagonistic behaviour were observed. It was found that some of the PBDE compounds with antiestrogenic activity remain in the bounded form in the channel of the ER rather than binding to the binding cavity, where compounds without anti-estrogenic binds. So, the study suggested the comparison

Table 2. Popular Docking Programs and Their Availabilities

Docking Tools	Availability
MacroModel 9.1	https://www.schrodinger.com/macromodel
Surflex-Dock	https://www.rdmag.com/product-release/2006/09/surflex-dock
ADT/Autodock tools	http://autodock.scripps.edu/resources/adt
CDOCKER module in Discovery Studio	accelrys.com
Fred version 2.2.25	https://www.eyesopen.com
Molecular Operating Environment (MOE)	https://www.chemcomp.com/Products.htm
GLIDE	https://www.schrodinger.com/glide
Molegro Virtual Docker (MVD, version 4.5.0)	https://molegrovirtualdocker.weebly.com
DOCK	http://dock.compbio.ucsf.edu/

of ligand binding pose is important in docking to confirm the anti-estrogenic activity of PBDE compound. The structural and conformational requirements in case of PBDE compounds when docked to hERα was evaluated by considering the docking score, hydrogen bonds interaction with amino acid residues, hydrophobic interaction, are considered as the key factors for estrogenic activity.[26,27] Docking simulations were performed between the endocrine-disrupting chemical xenoestrogen bisphenol A, and 271 receptor proteins related to different biochemical processes and revealed that the endocrine disruptors may have potential to interact with different targets other than endocrine receptors. The docked conformation was subsequently analysed by using Ligand Scout 3.0 tool and the interactions between those proteins and BPA were observed as mostly hydrophobic and specific hydrogen bonds formed by amino residues.[28] A computational modelling study by Butt & Stapleton was also proved about the inhibitory effect EDCs such as hydroxylated PBDE, triclosan, and other chlorinated, brominated, and iodinated analogues of 2,4,6-trihalogenated phenol and BPA, to the TH sulfotransferase a key enzyme of thyroid hormone metabolism. In addition to this, *in vitro* sulphotransferase inhibition study was carried out to confirm the result.[29] Molecular docking study by Kerdivel et al suggested that the benzophenone (BP) molecules firmly binds to the ERα in its ligand-binding pocket thereby exhibiting the anti-estrogenic activity. The strengthening of the stabilization in case of this binding interaction was observed due to consistent interaction of hydroxyl (OH) group at the phenyl ring of the ligand with the amino acids like Glu-353, Arg-394 and Phe-404 of the receptor molecule. The obtained results were found consistent with the experimental study consists of the proliferative assay to understand the capability of BP molecules to induce the proliferation of ERa-positive MCF-7 breast cancer cell line, controlled by estrogen hormone.[30] Similarly, computational docking analysis was used by Harris et al, to evaluate the endocrine disruptor property of the environmental contaminant such as PCB-30 (2, 4, 6-trichlorobiphenyl) by binding with the hER-α. This Computational method predicted that due to hydroxylation of PCB-30 occurs at the 3 or 4 position of phenol is responsible for stronger binding affinity in comparison to the parent molecule. Further *in vitro* P450 exposure and bioassay study was conducted by incubating *Saccharomyces cerevisiae* with PCB-30 and 4hydroxy-PCB-30 indicated that presence of the hydroxyl group at position C 4 on PCB-30 resulted in an approximately 1000 times increase in estrogenic response.[31] The docking computation was also used by Ng et al to discriminate between *agonistics* and *antagonists* EDC molecules involving ER as the target. The work was based on considering the available crystallographic structure of agonistic and antagonistic molecules available in the Protein Data Bank (PDB), followed by validating their features by literature and implementation of molecular docking methods to discriminate between the same with sufficient accuracy.[32] Computational docking study of 122 cosmetic compounds with 14 human nuclear receptor molecules was studied by Plošnik et al in 2015. The method involved in this work is the retrieval of crystallographic structures of 14 human nuclear receptors from the PDB and analysis of the factor responsible for direct binding of ligands to nuclear receptors to it. Subsequently, the binding interactions were predicted by using the online tool Endocrine Disruptome (http://endocrinedisruptome.ki.si/). Out of the 122 compounds, 21 were categorically predicted as the probable toxicants for endocrine disruption by observing the high binding affinity.[33] Similarly, in an experimental method followed by Zhang et al in 2015 resulted about the glucocorticoid and anti-glucocorticoid effects of 34 pesticides on human glucocorticoid receptor (GR) and further evaluated by luciferase assay.[34] The adverse reproductive effect of the Di (2-ethylhexyl) phthalate (DEHP) with progesterone receptor (PR) was analysed by *in silico* structural binding study and revealed about endocrine-disrupting potential of the molecules in normal PR signalling. The method consists of retrieval of the crystal structure of the human progesterone receptor (PDB ID: 1SQN) and ligands DEHP and derivatives, followed by docking simulation by using the program Glide (from Schrodinger). The result obtained as the hydrogen bonding is responsible for the stronger binding of the ligand and also pose confirmation on the receptor is similar to native ligand, hence can be considered as a potential PR disruptor molecule.[35] Comparative molecular docking study investigated the affinities of phthalates (a group of ubiquitous known environmental pollutants) and bisphenol A with selected human ketosteroid receptors, i.e., androgen (AR), progesterone (PR) and glucocorticoid (GR) receptors.

Molecular docking simulation was conducted by use of Glide tool to evaluate the molecular interaction pattern for the 31 ligands (consisting of 12 phthalates, monophthalates, and phthalic acid) with selected human ketosteroid receptors. The binding affinities were compared with that of corresponding natural steroids with the established endocrine-disrupting xenobiotic compounds such as BPA. From the result, it was obtained that especially the diphthalates and monophthalates molecules having the potential for anti steroidal activity due to their interaction to all types of receptors. Also, the crucial amino acids of the receptors responsible for interaction were identified in this work.[36] Similarly, the study conducted by Rehan et al in 2015 has shown the binding pattern for BPA derivatives with the ketosteroid receptors by using Dock version 6.5 program. The interactions of the ligand molecules with the receptor were observed to share an overlapped steroid scaffold. The structural basis of the binding study was conducted by considering the BPA and its derivatives such as 4-Methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene (MBP), and 4-(1,1,3,3-tetramethylbutyl)phenol) (OP) as ligand with AR and PR respectively by molecular docking simulations. The research revealed about the five novel interactions with the amino acids such as Leu at the position 701 and 704, Asn-705, Met-742, and Phe-764 in case of AR and four interacting residues Leu at 715 and 718, Met at 756 and 759 in case of PR in overlapped manner similar to the natural hormone.[37] The endocrine disruptor nature of Dioxins, as well as DLCs, have been evaluated by Khan et al in 2017 by using molecular docking programs. In this work, all total of 100 dioxins and DLCs were considered for docking with androgen (hAR), glucocorticoid (hGR), progesterone (hPR) and mineralocorticoid (hMR) receptor comparatively with the binding pattern of known EDC Bisphenol A. The hydroxyl group of the DLCs, was observed to have impact on the affinities for binding with the receptors. Moreover, the molecular forces responsible for the binding was observed as H-bonding, π-π stacking, hydrophobic, polar and van der Waals' interactions. In comparison to the BPA some of the DLCs reported showed high binding affinity hence can be predicted as more potential toxic compounds.[38] The endocrine disruption effect of bisphenol and their analogs on glucocorticoid biosynthetic pathway was analyzed by the molecular docking studies of 18 ligands with the selected enzymes of the pathway. The bisphenol M was observed to interact with the proteins involved in steroid hormone gene product like Cytochrome P450 family 11 subfamily A member 1 (CYP11A1) and Cytochrome P450 family 11 subfamily B member 2 (CYP11B2) significantly. Also, the compound Bisphenol PH (BP PH) was observed to have a significant affinity with 3α, 20β-hydroxysteroid dehydrogenase (3α/20β-HSD) enzyme.[39] Recently molecular docking was used to predict the reproductive toxicity of 139 chemicals with the interaction with nuclear receptors and subsequently validated by *in vitro* cell proliferation assay. In this work, the potential endocrine receptor-interacting chemical list was obtained from literature and further evaluated for their toxic effects by ToxCast server. Those compound shows a positive effect on the cell (immortalized human uterine endometrial adenocarcinoma cells) proliferation assay towards exposure to the compounds, were further subjected to binding analysis by computational docking method by taking ERα as a receptor to prove their effectiveness.[40] Similarly, another research work by Cotterill et al indicated the importance of implementing molecular docking method to identify the binders and non-binder ED compounds by considering the ERα as the receptor molecule. In this work, the binding energies of the selected compounds with ERα were computed by the molecular docking calculations followed by molecular dynamics simulation to know about the intrinsic activity. Further quantitative structure-activity relationship analysis was conducted to decipher the affinity of these compounds in a higher accuracy.[41]

Conclusions

Due to the hazardous effects of EDCs on human health, many attempts have been made to explore the mechanism of activity by using in-depth molecular level of research. However, to define, predict, rapid screening and to study the structure-activity relationship of EDCs at the molecular level is a difficult task in the experimental level due to the experimental cost and time frame of the study. Therefore, in this context, a computer-based molecular docking method plays an important role in the possible prediction of their molecular mechanisms concerning different endocrine receptor molecules. The binding features such as hydrogen bonding, pi-pi interaction and Vander walls force are predicted to be responsible for binding. Furthermore, due to the implementation of several potential molecular docking tools in the current research will provide great scope to study the endocrine-disrupting chemicals and their mode of inhibition with the hormone receptors. One of the major analytical aspects is to authenticate the mode of action of the EDCs to its receptor is that, whether it is due to the mimicking action of endocrine hormones or it interferes with the hormonal pathway (in the signal transduction process). In this way, the molecular docking can be also implemented to the discovery of novel molecules that exhibit endocrine disputing activity. Also, the binding pattern status of the EDCs with the different mutant form of receptors can be studied to access the real molecular actions by which this molecule interacts. Molecular docking study can be further analyzed by using molecular dynamics simulation to study effective binding and pose comparison of the potential compounds. In addition to this, the docking energy score can be combined with QSAR (Quantitative Structure Activity Relationship) methods to evaluate the prediction status for the compounds. Although molecular docking shows its efficiency in its prediction status, however this need to be subsequently validated by the experimental methods. Then the study will ultimately play a vital role in the risk assessment analysis on human health due to exposure of these toxic substances.

Conflict of Interest Disclosures

The author declares that he has no conflicts of interest.

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