Molecular Docking of Polycyclic Aromatic Hydrocarbons as Potentially Carcinogenic Molecules Through Binding with Aryl Hydrocarbon Receptor

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ABSTRACT. Aryl hydrocarbon Receptor (AhR) can activate gene target regulation through transcription, activation, or deactivation. Ligands for the AhR are mostly aromatic hydrocarbons. One of them is Polycyclic Aromatic Hydrocarbons (PAHs). These compounds are naturally found everywhere and are strong carcinogens. The purpose of this study was to perform a molecular docking analysis of three PAHs compounds (BaA, BaP, and PA) towards AhR to observe the strongest interaction in which could potentially lead to carcinogenesis. In this research, we retrieved the strongest three of the PAHs types: Benz[a]Anthracene (BaA), Benzo[a]Pyrene (BaP), and Phenanthrene (PA) from PubChem database. PyRx was used to minimize the ligands energy. Protein model of AhR (ID: 5NJ8) was obtained from PDB database. Discovery Studio Client 3.5 was used to remove water molecules and ligands attached to AhR. We interacted each ligand to the receptor by HEX 8.0.0 and visualized using Discovery Studio Client 3.5. We found that BaP, followed by BaA and PA, had the strongest interaction towards AhR. It indicated that BaP had a higher risk leading to cancer with more adverse effects compared to the BaA and PA interaction to AhR.

Keywords: Aryl hydrocarbon Receptor; Polycyclic Aromatic Hydrocarbons; carcinogen; molecular docking

INTRODUCTION

Aryl hydrocarbon Receptor (AhR) is a nucleat/steroid receptor of xenobiotics which can activate gene target regulation through transcription, activation, or deactivation [1]. When AhR is activated, it could facilitate the biotransformation and elimination of compounds which goes into the body from the air, water, and food. Xenobiotics, the ligands for the AhR, are mostly aromatic hydrocarbons. These aromatic hydrocarbons groups are for instance: Halogenated Aromatic Hydrocarbons (HaHs), Polychlorobiphenyls (PCBs), and Polycyclic Aromatic Hydrocarbons (PAHs) [2].

PAHs consist of carbon and hydrogen atoms in two or more aromatic rings. These compounds are naturally everywhere, mainly from volcanoes, forest fires, burning coal, car exhaust, and cigarette smoke [1]. Exposure to this compound is known to cause irritation of the eyes and breathing passages, as well as cancer due to its carcinogenic properties [3]. WHO reported that cancer is the second leading cause of death in the world. PAHs are strong carcinogenic compounds, which consist of many types. Some of these types have a greater risk of causing cancer than others. Based on this reason, we can comprehend the prominent of this research to be done.

In this research, we investigated the strongest three of the PAHs types: Benz[a] Anthracene (BaA),

Benzo[a]Pyrene (BaP), and Phenanthrene (PA). BaA consists of four benzene rings. BaP consists of five benzene rings. Meanwhile, PA consists of three benzene rings [1]. We are compared which of them that can act as cancer factor by performing *in silico* docking analysis of AhR (as a receptor) with the selected PAHs (as ligands). This was done by defining their bonding affinity, binding location prediction, or interactions.

METHODS

Ligands and Protein Receptor Preparation

The ligands such as BaA (CID: 5954), BaP (CID: 2336), and PA (CID: 995) were obtained from PubChem database as 3D-SDF format. PyRx was used to minimize the ligands energy and convert to PDB format. The protein model of AhR (ID: 5NJ8) was downloaded from PDB database. Discovery Studio Client 3.5 was used for preparing the receptor. We removed the water molecules and ligands attached to AhR.

Docking of Ligand-Protein and Visualization

HEX 8.0.0 was used to dock each ligand to the receptor. We predicted the possible interaction and energy binding of AhR with BaA, BaP, or PA (Table 1). The result was then visualized using Discovery Studio Client 3.5.

Table 1. Docking combinations between the receptor and ligand which was performed using HEX 8.0.0.

Ligand	Energy (kcal/mol)	Name	Distance (Å)	Category	Types
BaA	-232.9	:LIG1 – D:ARG143	4.84732	Hydrophobic	Pi-Alkyl
		:LIG1 – D:ARG143	3.88484	Hydrophobic	Pi-Alkyl
		:LIG1 – B:PRO327	4.63696	Hydrophobic	Pi-Alkyl
		:LIG1 – D:ARG143	4.31288	Hydrophobic	Pi-Alkyl
		D:ARG143:HE - :LIG1:H	1.23988	Unfavourable	Unfavourable Bump
		D:GLY144:HC - :LIG1:C	1.92828	Unfavourable	Unfavourable Bump
BaP	-230.6	A:ASP48:OD2 - :LIG1	3.47085	Electrostatic	Pi-Anion
		A:ASP48:OD2 - :LIG1	3.37140	Electrostatic	Pi-Anion
		A:ASP48:OD2 - :LIG1	3.40971	Electrostatic	Pi-Anion
		:LIG1 – A:ALA51	4.71448	Hydrophobic	Pi-Alkyl
		:LIG1 – A:ALA51	4.32373	Hydrophobic	Pi-Alkyl
		:LIG1 – C:LEU227	4.79783	Hydrophobic	Pi-Alkyl
		:LIG1 – C:LEU227	5.41073	Hydrophobic	Pi-Alkyl
		:LIG1 – A:ALA51	5.13129	Hydrophobic	Pi-Alkyl
		:LIG1 – A:LYS66	4.96237	Hydrophobic	Pi-Alkyl
PA	-191.93	:LIG1 – A:VAL69	5.43472	Hydrophobic	Pi-Alkyl
		A:LYS66:NZ - :LIG1	3.98893	Electrostatic	Pi-Cation
		A:LYS66:NZ - :LIG1	4.10921	Electrostatic	Pi-Cation
		:LIG1 – A:LYS66	4.46286	Hydrophobic	Pi-Alkyl
		:LIG1 – A:LYS66	3.78527	Hydrophobic	Pi-Alkyl

RESULTS AND DISCUSSIONS

The result of docking between Benz[a]Anthracene (BaA) towards AhR showed 6 interactions in total. The types of interactions were 4 non-bond interactions and 2 unfavourable non-bonds. The non-bond interactions indicated the Pi-alkyl interaction type which was categorized as a hydrophobic interaction. Three of the hydrophobic interactions were found between BaA and arginine-143 on the PAC domain of AhR, meanwhile one hydrophobic interaction was found between BaA and proline-327 on the PAS 1 (Per-Arnt-Sim 1) domain of AhR (Fig. 1). Each distance from the smallest to the largest was 3.88 Å, 4.31 Å, 4.63 Å, and 4.84 Å. Two unfavourable non-bond types yield distances within 1.24 Å to 1.93 Å, which occurred in the steric region. Van der Waals force usually contributes significantly to the cohesion energies and interfacial energies of solids and liquids. In these cases, Van der

Waals force determines the interactions occurring at interatomic spacings. This is where distance of the bonds and the energy are crucial [4].

The docking of Benzo[a]Pyrene (BaP) and AhR showed that there were 10 non-bond interactions. The non-bond interaction indicated that there were 3 bonds in the form of Pi-anions, all of the them were categorized as electrostatic interactions between the BaP and aspartic acid-48 on bHLH (basic helix-loop-helix) domain of AhR (Fig. 1). The other 7 non-bond interactions were Pi-Orbitals type. They were categorized as hydrophobic interactions. Five of the hydrophobic interactions were found between BaP and alanine-51, between BaP and lysine-66, and once between BaP and valine-69 on the bHLH domain of AhR (Fig. 1). Meanwhile two hydrophobic interactions were found between BaP and leusine-227 on the PAS 2(Per-Arnt-Sim 2) domain of AhR (Fig. 1). The longest distance of the non-bond interactions was 5.435 Å (hydrophobic), while the closest distance was 3.371Å (electrostatic).

Figure 1. The 3D and 2D structures of docking between BaA (top), BaP (middle), and PA (bottom) towards Aryl hydrocarbon Receptor (AhR). Binding location of the ligands is shown on the left column; AhR domains are shown in different colour as following: bHLH (red), PAS 1 (orange), PAS 2 (green), and PAC (blue). Middle column shows the ligand binding interactions between the ligand and amino acids of AhR

Phenanthrene (PA) and AhR complex established 4 non-bond interactions on the bHLH domain of AhR (Fig. 1). The non-bond interactions showed that there were 2 bonds, between lysine-66 of AhR and PA, which was categorized as electrostatic interactions. The other 2 bonds found were between PA and lysine-6 of AhR. Both of them were classified as hydrophobic Pi-alkyl interactions.

Based on our docking results, most of the interactions were hydrophobic interactions. Interactions from the strongest occurred, consecutively, in BaP, BaA, and PA. The non-covalent interactions (hydrogen and halogen bonding, van Der Waals forces, etc.) use much lower energy than the covalent one. However, regarding their multiplicity and facile transformation, the overall influence of a reaction can be decisive. The hydrogen bonds influence the reactivity of the substrate in various ways. For example, an oxygen

atom of a carbonyl group of a thioketone requires a strong bifurcated hydrogen bonding, the electrophilic character of the corresponding carbon increases toward the nucleophile attack, compared with a simple hydrogen bonding [5]. The same case can occur in this study, the hydrophobic interactions, combined with the electrostatic can produce a strong impact.

BaP and PA binds mostly onto the basic helix-loop-helix (bHLH) which functions as the DNA binding region of AhR [6]. The strong interactions indicate stronger impact for the greater downstream effect. When the ligand (PAHs) can bind to the protein (AhR) with a strong interaction, it can result in a greater damage of DNA transcription, which can lead to tumorigenesis and eventually to cancer. The heterodimer of PAHs-AhR and ARNT will bind to the XRE (xenobiotic responsive element) (where the heterodimer is recognized as a xenobiotic). This

heterodimer binding will control the modulation of the target expression which can lead to cancer [2].

CONCLUSION

BaP was the strongest carcinogenic PAHs compound, followed by BaA and PA due to its strong interaction with AhR. It might have a higher risk leading to cancer with adverse effects compared to the BaA and PA interaction to AhR.

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