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Molecular Docking and *In-silico* Studies of Lapachol and 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione Against Human Estrogen Receptor Alpha

Zulfa Hamid*

Department of Biotechnology, Mohammed Obeid Mobarak Laberatories, University of Gezira, Gezira, Sudan

Abstract

Breast cancer affects large number of women and the incidence of its occurrence is increasing annually. Human estrogen receptor alpha over expression known as one of the causes of breast cancer. Naturally produced medicinal compounds are well known for their efficacy and safety. In this study the focus is on two naturally occurring compounds which are found to have antitumor activities and they are found in a plant that has been used traditionally for breast cancer treatment for long time. These two compounds are Lapachol and 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione, Fulvestrant was used as a control. swissDock was used for docking of the three compounds against Human Estrogen Receptor alpha and then they were evaluated for their dug likeness properties. Lapachol and 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione showed slightly lower binding energy and better drug likeness properties than the standard. Showing that they can be farther investigated as oral anti Human Estrogen Receptor alpha agents.

Keywords: Docking • *In-silico* • estrogen • Lapachol • 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione

Introduction

Breast cancer is the most occurring type of cancer and the main cause of death associated with cancer among women [1]. Almost 70% of breast cancers express either estrogen receptor, progesterone receptor or both which are known as hormone receptor positive tumors [2].

Estrogen receptor has two main types' estrogen receptor alpha and estrogen receptor beta, which are controlling many physiological processes including the protection of cardiovascular tissue and the central nervous system, development of the female reproductive system and bone mass maintenance. Cancer occurrence in breast, ovarian and uterine tissue is believed to have many causes, and one of them is the dysregulation of estrogen receptor signaling within these organs which led to the discovery and development of anti-estrogenes as therapeutic agents [3].

Medicinal plants are believed to have many advantages over other products as anticancer agents, because of their safety, lack of toxicity and high availability [4]. *Kigelia Africana* has been used since time immorials as a traditional medicine for the treatment of cancer, skin disorders, gynecological infections, and other diseases. Lapachol and 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione are two compounds found in *Kigelia Africana* which are found to have antitumor activity [5].

Fulvestrant is a competitive estrogen receptor antagonist. It showed increased efficacy for the treatment of patients with HR+ve/HER2–ve advanced breast cancer, alone or in combination with other endocrine agents or targeted therapies [6].

***Address for Correspondence:** Zulfa Hamid, Department of Biotechnology, Mohammed Obeid Mobarak Laberatories, University of Gezira, Gezira, Sudan, Tel- 909765649; E-mail: Z.hamid55555@gmail.com*

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Molecular docking is an *insilico* structure based method widely used in drug discovery. It was firstly applied for molecular recognition between small and large molecules, now it is used for determination of novel therapeutic compounds, ligand-target interaction prediction and structure activity relationship (SAR) studies [7].

The aim of this study was to apply Insilco docking of Lapachol and 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione against Human Estrogen Receptor alpha, evaluate their drug likeness properties and to compare between the results of the two compounds and Fulvestrant as a control.

Materials and Methods

Protein preparation

The 3 dimentional crystal structure of Human Estrogen Receptor alpha with PDB DOI: 10.2210/pdb3ERT/pdb in complex with hydroxy Tomoxifen was retrieved from protein data bank (http://www.rscb.org/pdb).

Protein active site prediction

The prediction of the active sites of the Human Estrogen Receptor alpha was done using prankweb ligand binding site prediction online service (http://prankweb.cz), the binding pocket with the highest score was then chosen.

Ligand preparation

The three dimentional structures of Lapachol, 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione and Fulvistrant were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/)in SDF format. The SMILES of the three structures were obtained using the online OpenBable format converter (http://cheminfo.org/chemistry/cheminformatics/FormatConverter/index.html).

ADME properties

The ADME properties of Lapachol, 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione and Fulvistrant were obtained using ADME lab2 online service (https://admetmesh.scbdd.com/service/evaluation/cal).

Molecular docking

The docking analysis of Lapachol and 2-(1-hydroxyethyl)-naphtho[2,3-b]

furan-4,9-dione with Human Estrogen Receptor alpha was done using SwissDock online service (http://swissdock.ch). All the parameters used were selected by default except the x, y and z centers of the binding site which are chosen according to the selected binding pocket.

Result and Discussion

Figures 1 and 2 shows the 3D structure of Human Estrogen Receptor alpha and the 3D structure of its chosen binding pocket respectively. Table 1 represents the properties of the selected active pocket of Human Estrogen Receptor alpha.

The structures of Lapachol, 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione and Fulvestrant are shown in Figure 3, their PubChem CIDs, ZINC entries and physical properties are shown in Table 2.

The dug likeness properties of the three compounds are shown in Table 3. As it is shown 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione has the lowest LogP among the three compounds which indicates that it has the highest solubility followed by Lapachol and the least soluble is Fulvestrant. LogP of 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione lies in the range of the ideal LogP for oral drug which is (0 – 3).

Log D of Lapachol and 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione are 2.616 and 2.149 which is the ideal range for oral drugs (1-3), molecules with LogD in this range have good intestinal absorption because of their good solubility and passive diffusion permeability balance, and low binding to metabolic enzymes. While Fulvestrant has 4.769 LogD which indicates good permeability but low absorption due to its lower solubility and it has increased binding ability to metabolic enzymes, this is why Fulvestrant is only available as an injectable form [8]. The three compounds have Polar surface area (PSA) lower than 140Ao which is one of the requirements to pass Viber rule but unfortunately Fulvestrant doesn't have the other requirement which is having less than or equal 10 rotatable bonds as it contains 14 rotatable bonds.

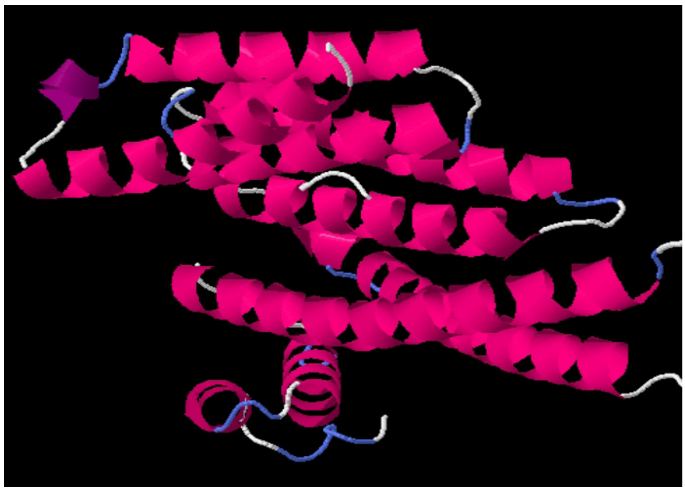

Figure 1. 3D Structure of human estrogen receptor alpha.

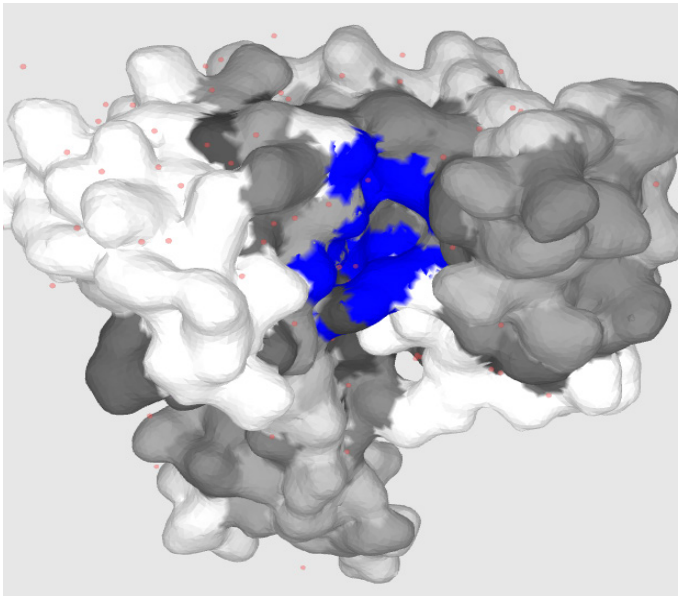

Figure 2. 3D Structure of human estrogen receptor alpha chosen binding pocket.

Table 1. Properties of the selected active pocket of target ER-alpha based upon top scores.

Pocket rank	Pocket score	Probability score	AA count	conservation	Surface atoms
1	11.22	0.632	15	2.051	34

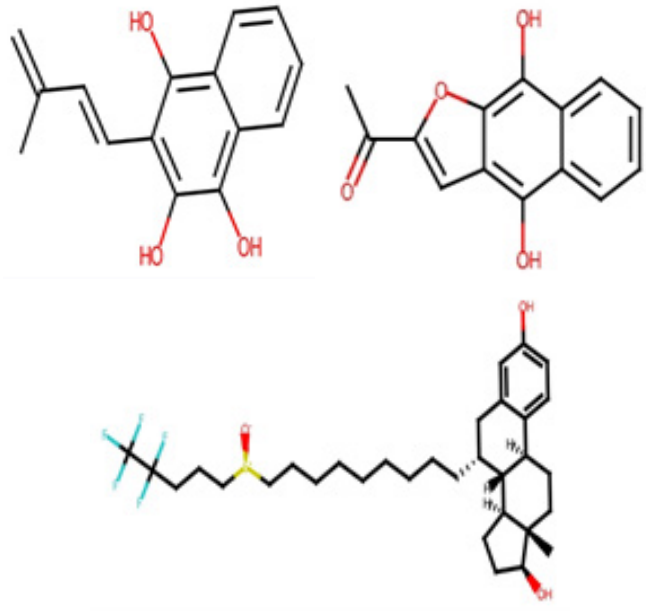

Figure 3. Structures of ligands A: Lapachol, B: 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione, C: Fulvestrant.

Table 2. Pubchem ID, zinc entry and other physical properties of Lapachol, 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione and Fulvestrant.

Name	Pubchem CID	Zinc entry	Molecular weight (g/mol)	Molecular formula	Hydrogen bond Donor	Hydrogen bond acceptor	Rotate able bond
Lapachol	3884	78934733	242.27	$C_{15}H_{14}O_3$	1	3	2
2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione	150068	6030303	242.23	$C_{14}H_{10}O_4$	1	4	1
Fulvistrant	104741	3926298	606.8	$C_{23}H_{47}F_5O_3S$	2	9	14

Table 3. Drug likeness properties of Lapachol, 2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione and Fulvestrant.

Name	logS	logP	logD	TPSA
Lapachol	-3.725	4.080	2.616	60.690
2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione	-3.446	2.861	2.149	70.670
Fulvistrant	-3.758	7.339	4.769	63.520

Table 4. Result of some of drug likeness rules for Lapachol, 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione and Fulvestrant.

Name	Lipinski Rule	Viber Rule	Golden Triangle
Lapachol	Accepted	Accepted	Accepted
2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione	Accepted	Accepted	Accepted
Fulvestrant	Rejected	Rejected	Rejected

Table 5. Docking results of Lapachol, 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione and Fulvestrant.

Name	FullFitness (kcal/mol)	Estimated ΔG (kcal/mol)	Element	Cluster
Lapachol	-1544.78	-7.10	0	0
2-(1-hydroxyethyl)-naphtho[2,3-b] furan-4,9-dione	-1508.30	-6.60	6	0
Fulvestrant	-1507.59	-9.12	0	2

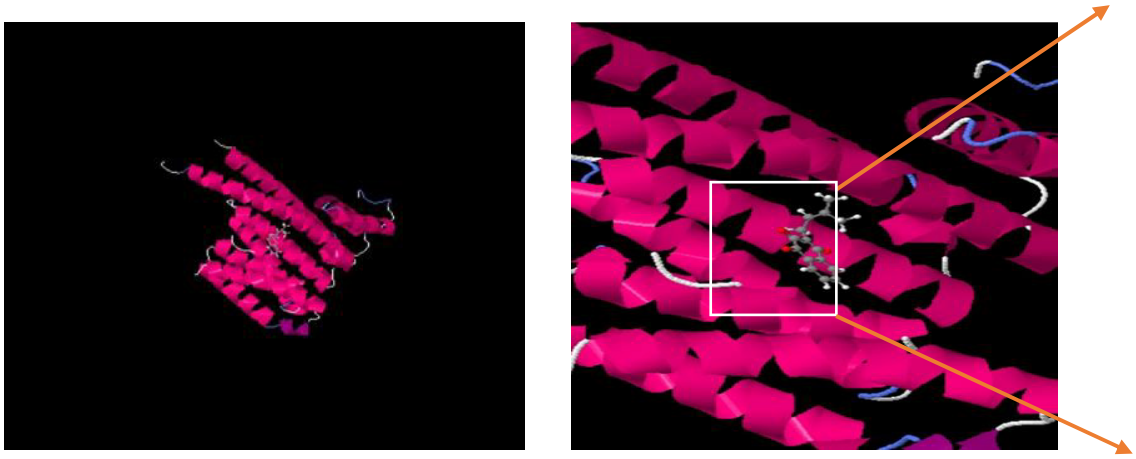

Figure 4. Docking of lapachol with human estrogen receptor alpha.

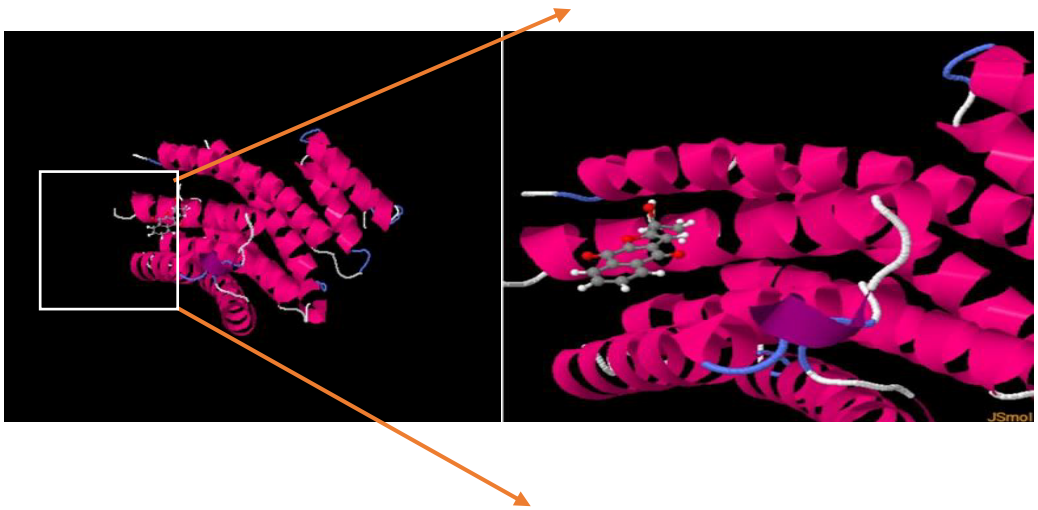

Figure 5. Docking of 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione with human estrogen receptor alpha.

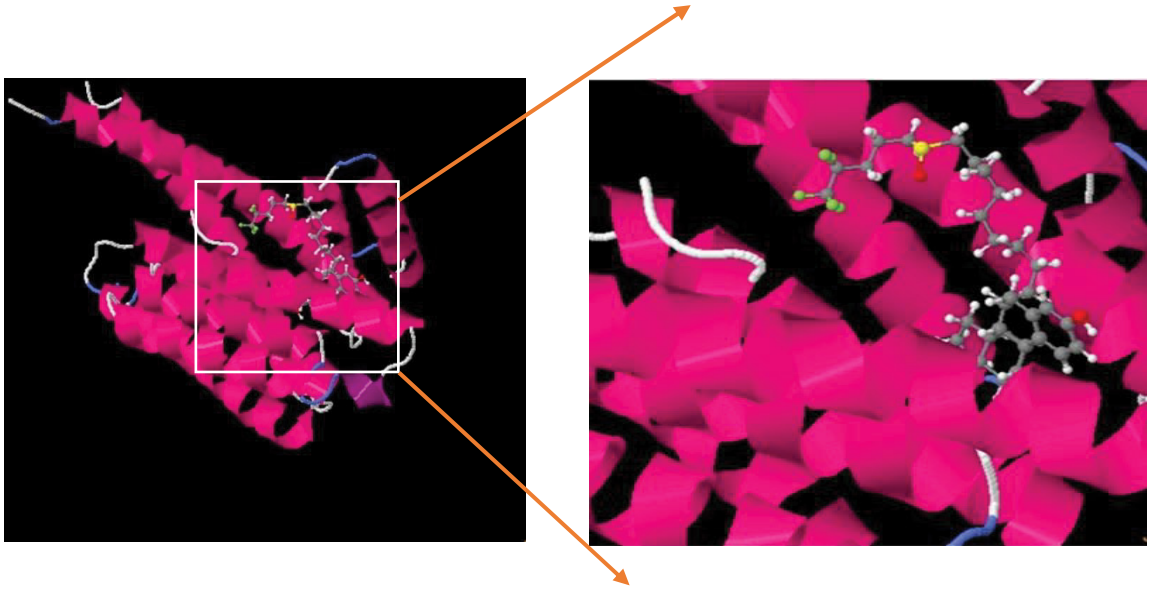

Figure 6. Docking of fulvestrant with human estrogen receptor alpha.

Table 4 represents the three compounds results against three of drug likeness rules. Lipinski rule and Viber rule are used to determine the absorption and bioavailability of the molecules. A molecule accepted by these rules has good oral bioavailability and can be used orally. As it appears in Table 4 Lapachol and 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione are both accepted by both rules while Fulvestrant is not accepted by any one of both rules [8].

Another drug likeness rule is Golden Triangle rule which indicates that when plotting molecular weight versus LogD (at pH 7.4) for a series of molecules it is noticed that compounds with favorable permeability and low clearance will be concentrated within a triangular shaped area called the Golden Triangle, which indicates that these molecules are metabolically stable and permeable. Lapachol and 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione were accepted by this rule while fulvestrant was rejected [9].

Table 5 shows the results of docking of the three compounds against Human Estrogen Receptor alpha. Lapachol had the highest full fitness energy followed by 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione their 3D docking is shown in Figures 4 and 5 respectively. The lowest full fitness energy was for Fulvistrant followed by Lapachol and then 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione. Despite that △G of Fulvistrant was the highest (-9.12), △G of Lapachol and 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione (-7.10) and (-6.60) respectively are not ignorable results can give recognizable pharmacological results and both of them have remarkable drug likeness properties and can be used successively as oral medications (Figure 6).

Conclusion

Medicinal plans are being used for ages for treatment of diseases and though the history they gave uncountable number of effective and safe medications. *Kigelia africana* extract have been used traditionally for breast cancer treatment, many studies assured the antitumor effect of *Kigelia africana* extracts. Lapachol and 2-(1-hydroxyethyl)-naphtho [2,3-b] furan-4,9-dione are compounds extracted from *Kigelia Africana* which have antitumor activities. In this study they showed noticeable anti HERα activity with very good drug likeness properties. They are suitable candidates to be studied as oral Human Estrogen Receptor alpha inhibitors.

Disclosure statement

Declorations of interest: none.

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