PHARMACOPHORE ANALYSIS OF ANTIHYPERTENSION COMPOUNDS

R.Mandhira Priya[1] and C. Zozimus Divya Lobo[2*]

Department of Chemistry, St. Mary's College (Autonomous), Thoothukudi
Affiliated to Manonmaniam Sundaranar University, Tirunelveli, Tamil Nadu, India

ABSTRACT

A Pharmacophore examination focused on hypertension was carried out using PyRx software in conjunction with the Zinc Pharmer database. We developed a strong pharmacophore model by utilizing important molecular characteristics linked to the control of hypertension, such as aromatic rings, hydrophobic areas, and hydrogen bond donors/acceptors. The discovery of possible lead compounds with the best interactions with the pharmacophore model was made possible by further virtual screening of the ZincPharmer chemical library. These results demonstrate the effectiveness of virtual screening techniques in conjunction with computational pharmacophore modeling in accelerating the identification of new antihypertensive drugs, thereby providing interesting directions for additional experimental validation and drug development initiatives.

KEYWORDS: Molecular Docking, Protein, Ligand, Antihypertension, Pharmacophore Study, ACE Inhibitor, PyRx, ZincPharmer, SwissDock.

1.INTRODUCTION

The most common type of cardiovascular disease and a significant public health issue in both developed and developing nations is hypertension. A growing number of patients are presenting at younger ages due to the disease. The most common "non-communicable disease" (NCD) in the world and a major contributing factor to death is hypertension[1].

1.1 Types of Antihypertensive Drugs:

Most common types of antihypertensive drugs are,

- Calcium Channel Blockers
- Diuretics
- Alpha Blockers
- ACE inhibitors
- Vasodilators [2]

In addition to ACE inhibitors, other drugs used to treat hypertension include beta-blockers, Ang II receptor antagonists, diuretics and calcium channel blockers. ACE inhibitors are thought to be the safest class of antihypertensive medications among these substances. For the treatment of hypertension, a combination of these medications is thought to be more

beneficial [3]. Pharmacophores can be used to find possible leads in structural databases (lead discovery), to create compounds with desired properties (lead optimisation), and to utilise pharmacophore fingerprints to compare and contrast different molecules.Additionally, it can be utilised to create predicted 3D QSAR models or align molecules based on the three-dimensional arrangement of chemical characteristics[4]. The most advanced method for determining and extracting potential interactions between a ligand-receptor complex is called pharmacophore modelling [5].

2.METHODOLOGY

2.1. Docking Interaction

The SMILES notation of phytochemical compounds from different medicinal plants, was collected. The 3D structures of these compounds were generated using PUB Chem software. Selected ligands are inserted into Lipinski's rule of five. We came to known about whether these ligands obey or not.The docking interactions revealing H-bond and Vanderwaals forces among the phytochemical compounds and the amino acid residues of were analyzed by PyRx-Python Prescription (PyRx).

2.2. PyRxDocking

PyRx is a Virtual Screening software for Computational Drug Discovery. PyRx enables Medicinal Chemists to run Virtual Sereening from any platform and helps users in every step of this process. From data preparation to job submission and analysis of the results. PyRx also includes chemical spreadsheet-like functionality and powerful visualization engine that are essential for structure-based drug design. Using pyrx can identify which ligand are bind high affinity with protein.

2.3. Zincpharmer

Pharmer pharmacophore search technology is used to search the ZINC database's purchasable chemicals. The structural arrangement of the key components of an interaction is described by a pharmacophore. Lead compounds for drug discovery are molecules that match a well-defined pharmacophore.

2.4. SwissDock

A web server called SwissDock is devoted to doing protein-ligand docking simulation in an elegant and user-friendly manner. SwissDock offers an easy-to-use, integrated interface and is based on the protein-ligand docking. The SwissDock sends back the results via email and lets the user upload structural files for both ligands and proteins. We can use the UCSF Chimaera programme to produce these input files, which will make it easier to submit the protein and ligand files.

3. RESULTS AND DISCUSSION

3.1 Ligand Preparation

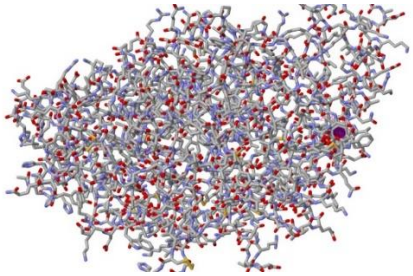
The three-dimensional structures of the phytochemical compounds, such as flavonoids and alkaloids, from different plants was done using ACD Chemsketch. With the use of the OPEN BABEL conversion and structure file generating server, the 3D structures of these compounds were created and translated into SDF format. The Lipinski Rule of Five helps in the differentiation of drug-like from non-drug-like compounds. It forecasts a high likelihood of success or failure due to drug resemblance.

S No	Name	Molecular Mass Less 500	H donor Less 5	H acceptor Less 10	LogP Less 5	Molecular Diffraction (40-130)	Obeys / Not
1.	(-)-Anaferine_443143	224	2	3	1.619900	65.524384	Obey
2.	Apigenin_5280443	270	3	5	2.419599	70.813881	Obey
3.	Arctigenin_64981	372	1	6	2.992399	99.551773	Obey
4.	BehenicAcid_8215	340	1	2	6.162793	121.062271	Not
5.	Bisdemethoxycurcumin _5315472	308	2	4	3.352699	88.912567	Obey
6.	Cesplon_44093	217	1	4	0.627900	55.387791	Obey
7.	Cosmosiin_5280704	432	6	10	0.107300	103.54425	Not
8.	Enalaprilatum_5462501	348	3	7	1.126100	91.155281	Obey
9.	FAPGG_6438387	399	4	9	0.337300	103.473869	Obey
10.	Forskolin_47936	410	3	7	1.519900	104.845352	Obey
11.	Fosfenopril_62956	435	2	6	4.161699	116.758057	Obey
12.	Gallic Acid_370	170	4	5	0.501600	38.395699	Not
13.	Glycyrin_480787	382	2	6	4.083299	105.958565	Obey
14.	Hentriacontane_12410	436	0	0	9.740998	171.590942	Not
15.	Lysinopril_5362119	405	5	8	1.235199	108.386665	Obey
16.	Moexipril_91270	498	2	9	2.351600	132.072479	Not
17.	Odrik_5484727	430	2	7	2.773300	116.414452	Obey
18.	Oxalacetate_164550	130	0	5	-3.554600	19.637999	Not
19.	Pterostilbene_5281727	256	1	3	3.579798	76.580780	Obey

20.	Quinapril_54892	438	2	7	2.334400	118.968452	Obey
21.	Ramipril Diacid_5464096	388	3	7	1.904701	102.800262	Obey
22.	Rutin_5280805	610	10	16	-1.878800	137.495483	Not
23.	Silibinin_31553	482	5	10	2.362700	119.449440	Obey
24.	Tocol,(2R)-_58866062	388	1	2	7.915003	120.179749	Not
25.	Vasicine_667496	188	1	3	1.296800	54.570793	Obey

3.2 Binding Site Prediction

Using the reference of the ligand complex in the recovered PDB file, the amino acid residues in the 4C2R protein's binding site are defined. It predicted binding site by using PyRx-Python Prescription or UCSF Chimera.



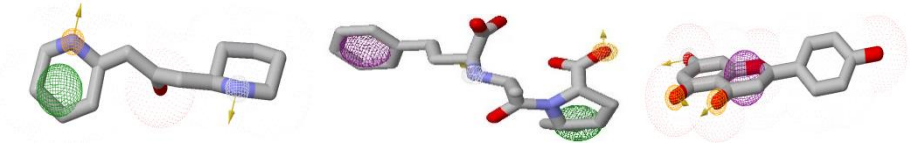
Based on blind docking, we get these binding affinity in PYRX between 4C2R protein with ligand molecules.

3.3 Pharmacophore

Further extended of our study of the docked ligand into a Pharmacophore analysis. Pharmacophore model of ligand represents spatial arrangements of ligands chemical features such as hydrogen bond donor and acceptors. That are necessary for binding to its ligand protein. Among so many software's available for Pharmacophore study, we chosen zinc pharmer for identifying best conformer of ligand.

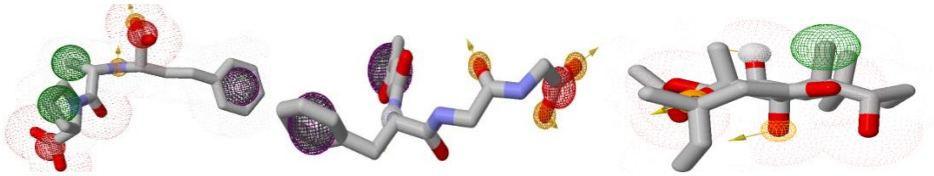
3.4 Zincpharmer

The structural arrangement of the key components of an interaction is described by a pharmacophore.The best conformer of ligand output in Zinc database are choosen to further discussion. Zincpharmer results are shown below,

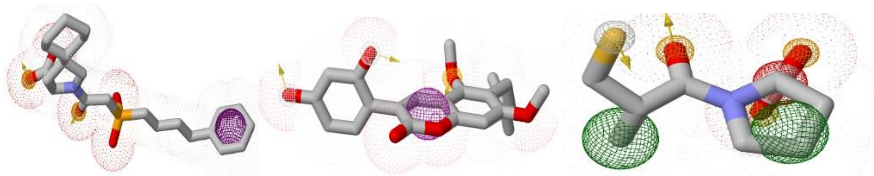


Anaferin **RamiprildiacidApigenin**

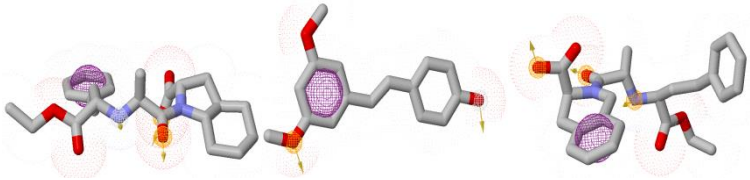
ArctigeninBisdemethoxycurcumin **Cesplon**



EnalaprilatumFAPGG **Forskolin**



Fosfenolatum **Glycyrin Lysinopril**



OdrikPterostilbene **Quinapril**

3.5 SwissDock

SwissDock is an online service that forecasts potential molecular interactions between a small molecule and a target protein. Swiss Dock accept the protein in PDB format. Pharmacophore best Zinc conformer is chosen as ligand. It accept the ligand in Zinc ID or ligand in mol2 file format. Now we get the Swiss binding affinity, between the protein and selected best conformer ligand. Visualization is done with UCSF Chimera.

Ligand Name	Ligand ID	Fit Value
Anaferine	ZINC90634043	0.509
Apigenin	ZINC90956202	1.0382
Arctigenin	ZINC80330482	0.6147
Bisdemethoxycurcumin	ZINC77303360	1.9683
Cesplon	ZINC22007503	3.1299
Enalaprilatum	ZINC41467453	1.8858

FAPGG	ZINC72060012	1.6405
Forskolin	ZINC63744111	1.0992
Fosfenopril	ZINC34888737	1.3748
Glycyrin	ZINC17201005	0.9273
Lysinopril	ZINC90187897	2.4038
Odrik	ZINC72939778	1.7770
Pterostilbene	ZINC84792602	0.5399
Quinapril	ZINC04182899	0.8078
RamiprilDiacid	ZINC94954526	1.7496
Silibinin	ZINC94655234	2.1229
Vasicine	ZINC92256347	0.2916

4. CONCLUSION

The virtual method of studying interaction of ACE inhibitor with ligands involves, the following steps.

Formatting protein (UCFS Chimera or BIOVIA**)**

To remove non residual parts in protein.

Calculating Binding Affinity (PyRx Server)

To study the interaction of receptor protein and ligand.

Selecting the best conformer of ligand (Zinc Pharmer)

To assess the best conformer of ligand (Zinc ID) for docking analysis.

Docking Analysis (SwissDock Online Server)

To identify the best fit value of ligand conformer with protein.

Thus, applying all these steps, the following ligands best fits into the protein (ACE inhibitor).

ZINC22007503,

ZINC90187897,

ZINC77303360,

ZINC41467453,

Based on this study, it could be concluded that above drugs with these conformer of ligand best suits for diseases related with hypertension.

5. REFERENCE

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