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Comparative Targeting and Molecular Simulation of the Newer Approached Berberine and Berberine Chloride

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Abstract - Our comparative observations with the model compounds and reference drugs between the wet lab and insilico methods opens up the hidden potential of the simple insilico approach for preliminary and faster screening of the new compounds using the angiogenic molecular targets. We approach to the navie molecule of designing with all its aspect like ligand and target interaction and lock key model to design the synthetic molecule for good resemblance of human health we find the better result and also suggestive for further study.

Keywords - Preliminary, Screening, Design, Ligand, Potential.

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1. INTRODUCTION

The development of an unknown compound to an effective anticancer drug takes a long scientific journey, efforts and money. In the past several decades, there have been numerous wet lab studies defining anticancer molecular targets which subsequently been validated by innumerable compounds in the wet lab. However, with the development of novel bioinformatics tools and softwares, it is wiser and advisable to use these relatively inexpensive and faster tools in the elucidation of mechanism(s) for novel compounds to be developed as anticancer drugs using specific molecular anticancer targets. Our approach was to validate the wet lab results of the model compounds (aeroplysinin-1, curcumin, halofuginone) along with some of the well-known anticancer.

2. MATERIALS

Proposed molecule to be studied

Berberine and its derivatives to be studied

Modification of the functional groups of berberine has a significant effect on the pharmacological activity. However, studies on altering the atoms and size of the berberine skeleton are rare. Thus, it may be beneficial to initiate a drug development program focused on inserting heterocyclic rings of different sizes into berberine According to the WHO report in 2020, there were approximately 19.3 million new cancer cases and nearly 10 million deaths, which were mainly attributed to lung, colorectal, liver, stomach, and breast cancers [1-3]. Under such circumstances, it is urgent to research the prevention and treatment strategies of cancers. The routine treatments for cancers are surgery, radiotherapy, and chemotherapy, but they showed limited actions with some adverse effects. The anticancer effects of natural products have become a research hotspot, due to their low or non-toxicity. Many studies showed that natural compounds from fruits, vegetables, tea, coffee, spices, and medicinal plants could play an important role in the prevention and treatment of cancers with different mechanisms of action. Berberine (Fig 1.) is a famous natural compound and exists in some medicinal herbs [4,5]. The chemical structure of berberine. Berberine shows many bioactivities, such as antioxidant, anti-inflammatory, cholesterol-lowering, antidiabetic, anti-obesity, and antimicrobial activities. In addition, its anticancer effects and mechanisms have been widely studied, and the results showed that berberine could be a promising

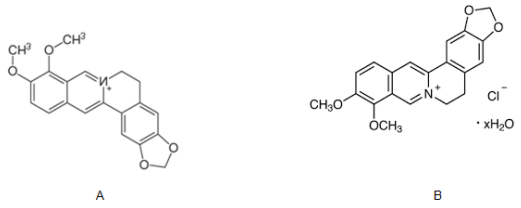

Figure 1: A-Berberine, B- Berberine chloride

All the docking studies have been carried out with the help of Growmax. Visualization of the molecules has been done through Accelrys Discovery Studio. The drug-likeliness and insilico toxicity studies have been checked through online bioinformatics softwares.

3. METHODOLOGY

Berberine and Berberine chloride, were checked against "The Lipinski Rule of Five", using the Lipinski Filter facility available online at Supercomputing Facility for Bioinformatics & Computational Biology, Indian Institute of Technology, New Delhi, India. The Lipinski's rule, formulated by Christopher A. Lipinski in 1997, is a rule to evaluate whether a given chemical compound with a certain pharmacological, biological and ADME (absorption, distribution, metabolism and excretion) activity, has the potential that would likely make it orally active drug in humans

Molecular modeling

Molecular docking experiments were performed using the AutoDock Tools 4.0 a suite of automated docking tool developed at the, which uses an empirical scoring function based on the free energy of binding [6-8] Genetic algorithms are the class of evolutionary computational models, in which the solution to an adaptative problem is spread among a genetic pool. In molecular docking, the solution corresponds to the best binding position and conformation for the ligand, and it is represented on a chromosome like data structure containing translation, orientation, and torsion genes. Basically, a genetic algorithm tries to mimic natural process of evolution and during this course gives rise to new generations until an optimum solution is achieved. The solutions are evaluated in terms of Binding energy (kcal/mol) and Inhibition constant (Ki). Morris et al., 1998). Among the stochastic search algorithms available on the AutoDock suite, we chose the Lamarckian Genetic Algorithm (LGA) which combines global search (Genetic Algorithm alone) to local search Solis and Wets algorithm to find the binding conformations of the ligand to the receptor. To achieve faster energy evaluation, AutoDock represents the macromolecule as a 3D grid, in which each point stores precalculated affinity potentials for all atom types of the ligand allowing flexibility to the ligand, while keeping the macromolecule rigid and fixed during docking.

Receptor finding

Crystal structures of EGFR (PDB ID: 2GS2), bFGF and VEGFR-2 in complex with motesanib (PDB ID: 3EFL) were retrieved from BrookHaven Protein Data Bank (www.pdb.org). The PDB files were energy minimized using GROMACS and the missing residues were corrected using repair missing atoms option available in AutoDock. The non-essential water molecules were removed and polar hydrogens were merged with the PDB file. The complexes bound to receptor molecule were further removed.

Ligand findings

As for the preparation of ligands, the molecular formula and SMILES notations for the known drugs like Berberine and Berberine chloride from PubChem data base and the three-dimensional structure was made by CORNIA and the co-ordinates of the ligand was searched from molecular network site to confer successful docking.

Docking studies

After preparing the receptor.pdbqt file and ligand.pdbqt file, the grid parameters file (.gpf) and docking parameters file (.dpf) were prepared. Based on previously reported structural information, grid across the active-site regions for the comparative AutoDock simulations of drugs Gefitinib and lapatinib drugs were considered standard against EGFR, while axitinib and motesanib were taken standard against VEGFR"s, for comparative study. The grid was sketched as 60* 60*62 with its grid centre 57.301 -0.505 -19.959 around EGFR, 36*42*54 with its grid centre 21.123 24.456 11.780 around bFGF, 70*70*68 around VEGFR-1 with its grid centre 5.987, 17.654, 33.321and 60*56*50 around VEGFR-2 with its grid centre 37.762, 33.456 17.123, as such that the ligand was allowed to rotate freely inside the grid. The genetic algorithm parameters in AutoDock were set to default values, by which the program itself determines the optimal run parameters depending on the nature of the ligand and the receptor active site. "Number of genetic algorithms runs", "Crossover frequency", and "Mutation rates" parameters were thus automatically adjusted by the AutoDock [9-12].

4. RESULT AND DISCUSSION

Our model compounds (Berberine and Berberine chloride) showed the drug likeliness properties within the recommended range, as suggested by Lipinski (Table 1). The molecular weights of all the three compounds were found to be below 500 Dalton and the H-bond donors within normal limit of 5 and H-bond acceptors existed within the desired range of 10 indicating that these compounds have drug-likeliness (Table 1). The log P values were also below 5 for all the three compounds.

Table-1 Molecular docking study score fitting Lipinski Rule

Molecule	Weight g/mol	H-bond acceptor	H-bond doner	Log P
Berberine	336.3612	4	0	-0.99
Berberine chloride	371.8	5	0	-0.45

Validation of Wet lab data with modeled compound on insilico study

Our docking simulation studies using the current anti-angiogenic molecular targets of EGFR, bFGF and VEGFR-1(Table 2) with the model test compounds and reference drugs produced promising

results in terms of binding energies (kcal/mol) and inhibition constant (µM)

Table 2 Docking Simulation Study Showing score of targets of VEGFR & EGFR,

Molecules	VEGFR			EGFR		
	B. energy	Inhibition constant	H-bonds	B. energy	Inhibition constant	H-Bond
Berberine	-5.12	564.10	2H	-3.63	1248.02	3H
Berberine chloride	-5.32	598.32	3H	-3.99	1356.09	3H

VEGFR- It seen from the compound score that the binding energy is moderate and they have good inhibition rate in comparison to other samples so that they can be suggesting for good anticancer activities they are suggesting an anticancer compound by the suggested scores.

EGFR The inhibition constant of Berberine was found to be 3.63 µM which was almost 86-fold less than curcumin and 200-fold less than aeroplysinin-1 suggesting berberine to be the strongest anti-angiogenic compound in agreement with the results shown. Further, gefitinib, lapatinib and axitinib produced binding energies against EGFR with respective values as represented in figure with different protein like tyrosine isoleucine aspergenine etc.

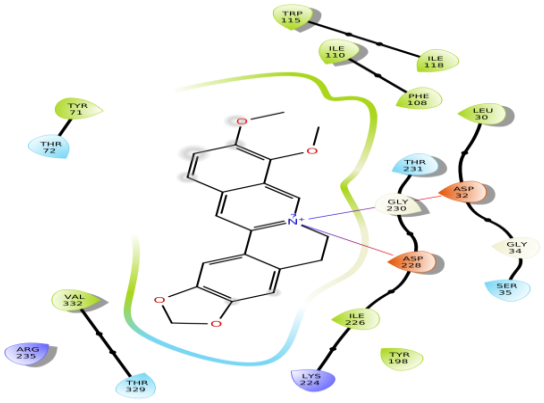

Figure 2: The docking structure diagram of berberine

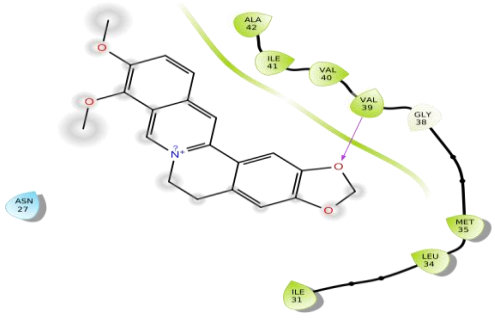

Figure 3: Docking structure of berberine chloride

Screening and validation and mechanism of action

Most of the anti-angiogenic drugs currently administered for treatment of cancer are already being withdrawn from the market due to the associated side-effects like hypertension and proteinuria which are the class effects of anti-VEGF drugs, while others have failed to prove their prolonged survival rate in the clinical trials. Furthermore, these drugs lack expected efficiency and have to be administered in combination with other drugs for proper therapeutic effect. Lapatinib is administered to the patients along with capecitabine which itself induces nausea, diarrhea and hand and foot syndrome. Some of these drugs like sorafenib were even clastogenic and mutagenic.

5. CONCLUSION

Furthermore, our insilico docking results clearly suggest for the first time that the steroidal alkaloid aglycones remarkably possess specific RTKs inhibitory capability in comparison to standard drugs which makes them as potential new generation natural anti-angiogenic drugs with little or no toxicity. We can move further for the processing and make feasible to prepare in laboratory to confirm its more effectiveness to the human health.

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