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In-Silico Studies of Oncogene Protein with Anti-Cancer Drugs

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Abstract: An oncogene protein (PDB I.D-5P21) has the possible for cause of cancer. In tumour cells, they were often mutated or expressed at very high levels. Mostly normal cells experience a programmed form of death (apoptosis). It is an important and striking target for anticancer drug development and discovery. In this course we have selected about 20 anticancer drugs that target the oncogene protein. However, the appearance of resistance to these anti-cancer drugs reduces the efficiency of the cancer by targeting the oncogene protein. Among the drug resistance, different sites have been identified for binding of the anti-cancer drugs i.e. Gly 13, Gly 15, Val 20, Asp 33 and Lys 117, which are basically important due to their resistance to nearly all the inhibitors in clinical development. A detailed appreciative of drug resistance mechanism to oncogene protein (PDB I.D-5P21) is critical for the design of novel potent agent targeting of oncogene protein of cancer. In this work, firstly we have to performed the molecular docking studies of about 20 anti-cancer drugs to the oncogene protein and calculate the negative binding energy of the docked complex of oncogene protein and anti-cancer drugs, which can be further studied by the simulation interaction. Molecular dynamics studies can be performed by Schrodinger-Desmond, to perform the possible outcomes under in-silico experiments with the oncogene and drug complex. Binding free energy reveals the drug resistance of anticancer and finds the interaction between the active site and substrate of oncogene and cladrabine. These findings can provides useful information for understanding the drug resistance mechanism beside the oncogene protein. This result also provides some latent clues for further design of novel inhibitors that are less suitable for the drug resistance.

Key words: Oncogene Protein · Anticancer Drugs · Molecular Docking and Molecular Dynamics

INTRODUCTION

When certain normal genes have developed a mutation in most of the oncogenes are known as proto-oncogenes. Proto-oncogenes are the genes that mainly control what type of cell it is and how often it divides [1]. When a proto-oncogene creates mutation (Changes) into an oncogene, it turns out to be a "bad" gene that can permanently change or activated when it is not invented to be. This leads to uncontrolled growth of cell, since cause the cancer. A few cancer syndromes are developed through inherited mutations of proto-oncogenes that cause the oncogene to be turned on (Activated). For example, multiple endocrine neoplasia type 2 (MEN2) is developed by an inherited mutation in the gene known as RET. People affected by this syndrome which develop an unusual thyroid cancer called medullary cancer of the thyroid. Mostly cancer-causing mutations concerning oncogenes are acquired, not inherited. They mainly stimulate the oncogenes through chromosomal rearrangements, gene repetition, or mutation. Tumour suppressor genes have normal genes that reduce the cell division, repair DNA mistakes, or tell cells when to die (This process is called as apoptosis or programmed cell death). Improper function of tumour suppressor genes reveals the cells can produce out of control, since lead to cancer [1, 2].

Some changes (Mutations) of gene could be inherited, which can increase the chances of developing cancer. Some mutations in oncogenes and tumour suppressor genes have been used to take decision for which people are maximum chances for developing certain types of cancers [3]. If the person have known that they carry a certain mutant gene, they may take certain

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precaution to minimize the chances. Suppose women who take a mutation in any BRCA genes have maximum chances of getting breast cancer. These women have advised to begin screening for breast cancer at a younger age by MRI along with mammography which can be help to diagnose breast cancer early. Some women even have surgery to reduce their risk of cancer [4-6]. In case of chronic myeloid leukaemia (CML), the cancer cells have a gene change called BCR-ABL that makes a tyrosine kinase (protein). Dosage form that target the BCR-ABL protein, such as imatinib (Gleevec ®), dasatinib (Sprycel ®) and nilotinib (Tasigna ®) etc, are often very effective against chronic myeloid leukaemia (CML). They reveal remission of the leukaemia in various patients treated in the early stages of their disease [7-9].

Hypothetically inhibition of tumour suppressor genes that exist via promoter hyper methylation could be initiated and regulated through the activation of oncogenes, explaining in fraction how a single oncogene can result in cellular transformation [10]. To evaluate this hypothesis we intended a model to diagnose tumour suppressor genes potentially regulated by oncogenes through methylation events [11]. We used the cellular model of v-src-mediated cellular transformation to estimate these relationships. In previous examination the genes that have mainly up-regulated by v-src and, in fact, enable to develop a 'Src fingerprint' of genes commonly regulated through Src that has been detected in human colon cancer specimens well known to harbour top levels of Src activity. In recent study genes are examine down-regulated through v-src to observe the relationship of tumour suppressor genes to the v-src oncogene. We estimated that a single oncogene, v-src, can inhibit the expression of various genes during the process of cellular transformation [12, 13].

Materials: In the present study, used different biological databases like PubChem, Drug Bank, PDB (Protein Data Bank) and software's like Auto-dock and Chemdraw. The PDB (Protein Data Bank) is the single universal Structural data of Biological macromolecules. It contains Structural evidence of the macromolecules determined by X-ray crystallographic, NMR methods etc. Auto-dock offers rather good on-screen molecule-building facilities, with a moderate library of useful molecules. It is a free molecular modelling package that scores under Windows.

Methods

Preparation of Protein Structure: Bioinformatics is seen as an emerging arena with the potential to significantly progress that how drugs are found and are brought to the clinical trials. Protein objective were downloaded from database Protein Data Bank (PDB). 5P21 is PDB id of the target protein. All water molecules were detached and on final stage hydrogen atoms were added to receptor molecule.

Preparation of Ligand Structure: 20 anti-cancer drugs were selected as ligand considering their biological activities (Methotrexate, vincristine, vinblastine, amifostine, amscarine, azacitidine, busulfan, carmustine, podophylotoxin, cladrribine, dacarbazine, doxorubicin, fluorouracil, flutamide, ifosfamide, mercaptopurine, mitotane, pentoatatine, tamoxifen and etopside)

The 3D structures of these anti-cancer compounds were found by using "Chemdraw". The docking analysis of anti-cancer drugs and oncogene protein (PDB I.D-5P21) was conceded by Auto-dock software. Docking permits virtually screening a database compounds and predicting the solidest binders based on their scoring functions. It explores ways in which two molecules, such as drugs and an oncogene protein receptor fit together and dock each other well. The molecules binding to a receptor, hinder its function and thus act as a drug [13]. Anti-cancer drugs and oncogene protein receptor were identified via docking and their relative strengths were evaluated using molecular dynamics and their binding affinities using free energy simulations. Anti-cancer drugs were docked with the oncogene protein receptor using parameters by default in Auto-dock software.

Protein Ligand Interaction Using Auto-Dock 4.0: Auto-dock is the electronic structure program that is based on the quantum mechanics, it foretells the potential energies, molecular structures; geometry optimization of structure, vibration frequencies of coordinates of atoms, bond length, bond angle and reactions pathway [14, 15].

Oncogene protein receptor was docked against the obtained ligand obtained using Auto-dock 4.0 to find the reasonable binding geometries and discover the protein ligand connections. Docking of the protein ligand complex was mainly targeted only on to the predicted active site. Docking simulations were performed by selecting "Auto-Dock" as the docking engine. The selected residues of the receptor were defined to be a part of the binding site [16].

Interaction Studies: The goal of ligand-protein docking is to predict the principal binding model(s) of a ligand with a protein of known three dimensional structures. To study

the binding modes of bioactive compounds in the binding site of oncogene 5P21 Protein, intermolecular flexible docking simulations were performed and energy values were considered from the docked conformations of the 5P21 -inhibitor complexes. Docking studies yielded crucial information regarding the orientation of the inhibitors in the binding pocket of the objective protein [17, 18].

Docking results of the ligands and its derivatives via Auto-dock software reveals that the binding energy of these drugs can be compared with the receptor.

Molecular Dynamics: Molecular dynamics (MD) simulations for proportional analysis, refinement and check stability of docked complex of Dendrimer were performed using Desmond 3.5 as instigated in Schrödinger package with 20.0 ns (Nanoseconds) simulation time [19]. The initial steps of MD simulations were performed by applying OPLS 2005 molecular mechanics force field. The temperature in the simulation experiments was 300K and the resulting trajectory length for each structure was 4.8 [20]. Simulation experiments were performed using periodic border line situations and the number of molecules N, pressure P and Temperature T were kept constant. The homology model was static initially and the energy of the system was minimized 10 (Minimum) steps using steepest descent algorithm (SD) and 50000 steps using conjugate-gradient algorithm (CG). Minimized system was heated from 0 to 300 K by velocity rescaling for 100ps and equilibrated 100ps in the NVT and 100ps in the NPT [21, 22]. Throughout the simulation the length of bonds involving hydrogen was constrained using LINCS algorithm. NPT ensemble, without restraints, for a simulation time of 24 ps (Temperature 300K) was performed to relax the system. The relaxed system was simulated for a simulation time of 10000 ps with a time step of 2 femtosecond (fs), NPT ensemble using a Berendsen thermostat at 300 K and velocity resampling for every 1ps. Trajectories after every 4.8 ps were noted. Energy fluctuations and RMSD of the complex in each trajectory were investigated with respect to simulation time [23].

Molecular Dynamics Simulation Experiment: In the molecular dynamic simulation was used two 3D structure of oncogene docked with virtually screened anti-cancer compounds.

Protein Preparation: Import a 3D Structure of oncogene-drug (Docked complex with drug) into Maestro and then prepare for simulation by using protein preparation wizard and shot all errors if any, assign hydrogen bond and set correct bond orders. The bond orders were assigned to residues of proteins, hydrogen atoms were added and tautomer states taking place at their normal pH (7.0).In System builder menu Set up membrane model POPC (PalmitoylOleoylPhasphatidyl Choline).Water molecules were located to the references structure with simple point charge (SPC) water model. System was neutralized with counter ions, SHAKE algorithm [24] used to constrain the geometry of water molecules and heavy atom bond lengths with hydrogen's [25], electrostatic communications applied using particle mesh ewald (PME) method and periodic boundary situations (PBC) Orthorhombic were used. In the system builder, size of solute is 39.995432-A, 73.88354-A, 50.973106-A and boundary condition of membrane system is Orthorhombic 59.995432, 93.88354, 65.477. Eliminating the membrane molecules that overlap the solute in reference structure and docked complex then it contains ……. membrane molecules. Eliminating the membrane solvent molecules that overlap the solute and finding solvent molecules in the omitted regions and then removing solvent molecules that overlap ions and no. of solvent molecules in system builder. Minimization was supported out using the OPLS (Optimized Potentials for Liquid Simulations) 2005 molecular mechanics force field with cut off RMSD(Root Mean Square Deviation) of 0.3 Å [26]. Full system minimization with restraints on solute was achieved for maximum 50000 iterations of a hybrid of the steepest descent and the limited memory Boyden - Fletcher - Gold farb-Shanno LBFGS) algorithms, without any restraints was accomplished with a convergence threshold of 20.0 kcal/mol/Å.2 Non hydrogen solute atoms were reserved in the NVT ensemble (Constant number of atoms N, volume V and temperature T) using 20 picoseconds (ps) simulation time and temperature of 10K. Simulations restrictive non hydrogen's solute atoms were executed in the NPT ensemble (Constant number of atoms N, pressure P and temperature T) for 12 ps simulation time and temperature of 10K. Further, NPT ensemble for a simulation time of 1.2 ps restraining all no hydrogen solute atoms (Temperature 300K)

RESULTS AND DISCUSSION

Molecular Docking: Molecular docking studies were performed with auto-dock tool and for this docking of oncogene protein (PDB I.D-5P21) was docked with 20 different anti-cancer drugs and calculated the binding energy of these complex structure. When all the compounds shoes the binding energy with the oncogene

protein some complex shows positive and some shows negative energy but we have selected only negative energy because only negative energy shows the excellent binding to the receptor compound. From this analysis we have selected highest negative binding energy complex with the protein and finally the cladribine has been taken from the listed docked compound. We have taken the selected drugs and oncogenes protein and docking can be performed, firstly the oncogene protein was docked with amifostine and binding energy was found to be -4.77 Kcal/mol then after amscarine binding energy and was found to be +49.20 Kcal/mol here the binding energy was found to be the positive value and only negative values was considered for binding to the protein. azactidine was docked with the protein the binding energy was obtained due to this complex was -6.23 Kcal/mol then again busulfan was docked and energy was obtained to be -5.59 Kcal/mol, carmustine was complexes with oncogene protein and energy was found to be -6.45 Kcal/mol, phodophylotoxin was docked and energy was obtained by the docking was +71.08 Kcal/mol, binding energy of cladribine with oncogene protein was obtained -7.17 Kcal/mol. Binding energy of docarbazine was obtained to be -6.02 Kcal/mol, binding energy of doxorubicin was obtained to be +905.43 Kcal/mol, binding energy of etopside was found to be +1.10 Kcal/mol, binding energy of fluorouracil was found to be -5.05 Kcal/mol, binding energy of flutamide was found to be -6.22 Kcal/mol, binding energy of ifosfamide was found to be -5.45 Kcal/mol, binding energy of mercaptopurine was found to be -5.33 Kcal/mol, binding energy of methotrexate was found to be +21.77 Kcal/mol, binding energy of mitotane was found to be -6.81 Kcal/mol, binding energy of pentostatine was found to be -6.32 Kcal/mol, binding energy of tamoxifen was found to be =261.58 Kcal/mol, binding energy of vinblastin was found to be +1.14 Kcal/mol and binding energy of vincristine was found to be +4.72 Kcal/mol. The binding energy was obtained with the docking of protein and ligand complex, here only negative binding energy was considered which can interact by H-bonds.so from the binding energy cladribine shows the lowest negative binding energy which can highly interact with by the H-bonds.

Cladribine was found to bind at binding site of oncogene protein with highest negative binding energy -7.17 Kj/Mol. Free energy of binding is calculated as a sum of four energy terms of intermolecular energy (van der Waals, hydrogen bond, desolvation energy and electrostatic energy), total internal energy, torsional free energy and unbound system energy. The major interactions shown in the oncogene protein binding site and cladribine are the important H-bonds with residues:Gly 13,Gly 15, Val 20, Asp 33 and Lys 117. These results suggest that cladribine have very high affinity for binding site of oncogene protein and probably act as competitive inhibitor as shown in Table1.

In Figure 1 we can seen the interaction of cladribine with the oncogene protein a, b, c from the different angles shows the binding of clodribine-oncogene protein complex structure. Where as in Figure 2 we can see that the binding site of anti-cancer drugs to the oncogene protein. Figure a, c, d, e, g, h, k, l, m, n, p and q shows the interaction with the oncogene protein and the anti-cancer drugs and have the lowest negative binding energy, while the other like b, f, i, j, o, r, s and t shows the positive binding energy but only negative binding energy shows the positive interaction with the protein-ligand interaction while positive binding energy will not shows the positive interaction.

Molecular Dynamics: The oncogene-anticancer complex with the leading negative binding energy obtained using Auto-dock was used for carrying out MD simulation. The structural dynamics of oncogene protein bound with anticancer drug were analyzed by performing 20 ns MD simulation. The system stability and overall convergence of simulations was monitored in terms of root-mean-square deviation (RMSD) for all backbone atoms, potential energy profile as well as the average residue fluctuations of the residues (RMSF). RMSD trajectory of backbone of oncogene-anticancer drug complex was calculated at every 0.5 ps using its initial structure as a reference.

Fig 3(a). Shows that the RMSD trajectories were always less than 2.5 Å for the entire simulation suggesting the stability of simulation system. The trajectories were equilibrated after about 2500 ps. In all these cases no great difference in trajectory was found but both backbone and c-alpha are related to each other. At 5 -15 ns these all show stability in the RMSD plot. Potential energy profile obtained for all MD simulation production run also showed very stable profile. In oncogene-cladribine complex potential energy remains stable about the average value of - 57600 Kj/Mol (Fig. 3(b).

Figure shows that interaction between backbone atoms and ligand, (a) represent the total interaction between the ligand and backbone atom at 20 ns time interval and shows a great stability at 0.8-1.2 Å, (b) shows that no interaction can be shown between the ligand and

Table 1: Energy table of oncogene protein (PDB I.D- 5P21) with anti-cancer drugs

S.no	Protein + Drug	RMSD (A)	Binding energy (Kcal/mol)	Inghibition constant (Um,Pmm)	Intermolecular energy (Kcal/mol)	Vdw+Hbond+ desolv energy (Kcal/mol)	Electrostatic energy (Kcal/mol)	Final total initial energy (Kcal/mol)	Torsional energy (Kcal/mol)	Unbound system's energy (Kcal/mol)
1	5P21 + Amifostine	38.921	-4.77	317.10 uM	-6.68	-5.02	-1.84	-0.38	+2.09	-0.38
2	5P21 + Amscarine	37.273	+49.20	170.79 uM	+48.30	+48.29	+0.02	+4.31	+0.89	+4.31
3	5P21 + Azacitidine	38.192	-6.32	23.11 uM	-6.92	-6.99	+0.07	-0.19	+0.60	-0.19
4	5P21 + Busulfan	38.210	-5.59	79.87 uM	-7.68	-7.33	-0.35	-0.47	+2.09	-0.47
5	5P21 + Carmustine	38.232	-6.45	18.59 uM	-7.95	-7.94	-0.01	-0.44	+1.49	-0.44
6	5P21 + Podophyllotoxin	35.374	+71.08	——	+69.89	+69.76	+0.13	+10.77	+1.19	+10.77
7	5P21 + Cladribine	37.581	-7.17	5.9 uM	-7.75	-7.66	-0.09	-0.09	+0.60	-0.09
8	5P21 + Dacarbazine	37.538	-6.02	38.49 uM	-7.22	-7.10	-0.11	-0.33	+1.19	-0.33
9	5P21 + Doxorubicin	24.138	+905.43	——	+905.43	+905.15	+0.28	-0.27	+0.89	-0.27
10	5P21 + Etoposide	25.996	+1.10e+03		+1.10e+03	+1.10e+03	+0.20	+8.61	+1.49	+8.61
11	5P21 + Fluorouracil	37.020	-505	200.39 uM	-5.05	-4.93	-0.11	+0.00	+0.00	+0.00
12	5P21 + Flutamide	37.279	-6.22	27.60 uM	-6.82	-6.83	+0.01	-0.23	+0.60	+0.23
13	5P21 + Ifosfamide	38.017	-5.45	102.00 uM	-6.34	-6.36	+0.02	-0.32	+0.89	-0.32
14	5P21 + Mercaptopurine	37.177	-5.33	123.73 uM	-5.33	-5.12	-0.21	+0.00	+0.00	+0.00
15	5P21 + Methotrexate	36.607	+21.77	——	+19.08	+19.08	+0.00	+5.97	+2.68	+5.97
16	5P21 + Mitotane	37.104	-6.81	10.20 uM	-7.11	-7.11	-0.00	-0.32	+0.30	-0.32
17	5P21 + Pentostatine	57.368	-6.32	23.29 uM	-6.92	-6.83	-0.09	-0.10	+0.60	-0.10
18	5P21 + Tamoxifen	25.468	+261.58	——	+259.79	+259.81	-0.02	-0.73	+1.79	-0.73
19	5P21 + Vinblastin	25.680	+1.14e+04	——	+1.14e+04	+1.14e+04	+0.14	+1.14	+0.89	+1.14
20	5P21 + Vincristine	28.708	+4.71e+03	——	+4.71e+03	+4.71e+03	-0.28	+149.57	+2.39	+149.57

backbone atoms at 0-2 ns,(c) at 3-19 ns interaction can be shown between ligand and backbone atoms,(d) Highest interaction can be noticed at 5-14 ns and shows closed attachment can be observed, (e) slightly variation between ligand and backbone atoms were observed at 14-19 ns and (f) at last no interaction can be found between ligand and backbone atom between 19-20 ns. When molecular dynamics can be performed at the initial state the molecules are not ligand excited but after some time when molecules are excited they comes together and form a stable complex of ligand-backbone and at the end again ligand and backbone move far from each other.

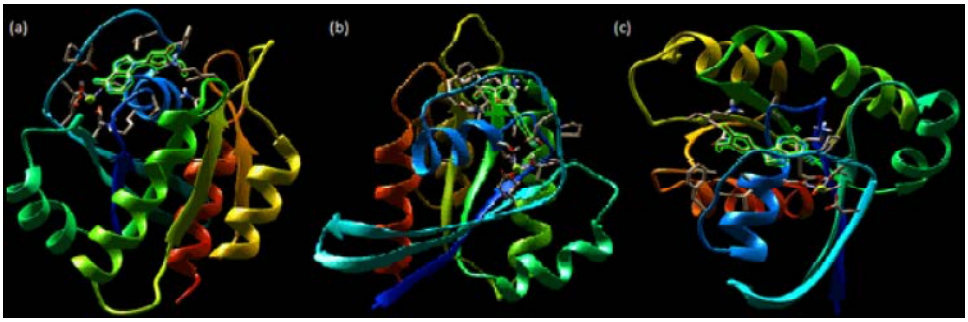

Fig. 1: Binding site of oncogene protein (PDB I.D-5P21) with Cladribine

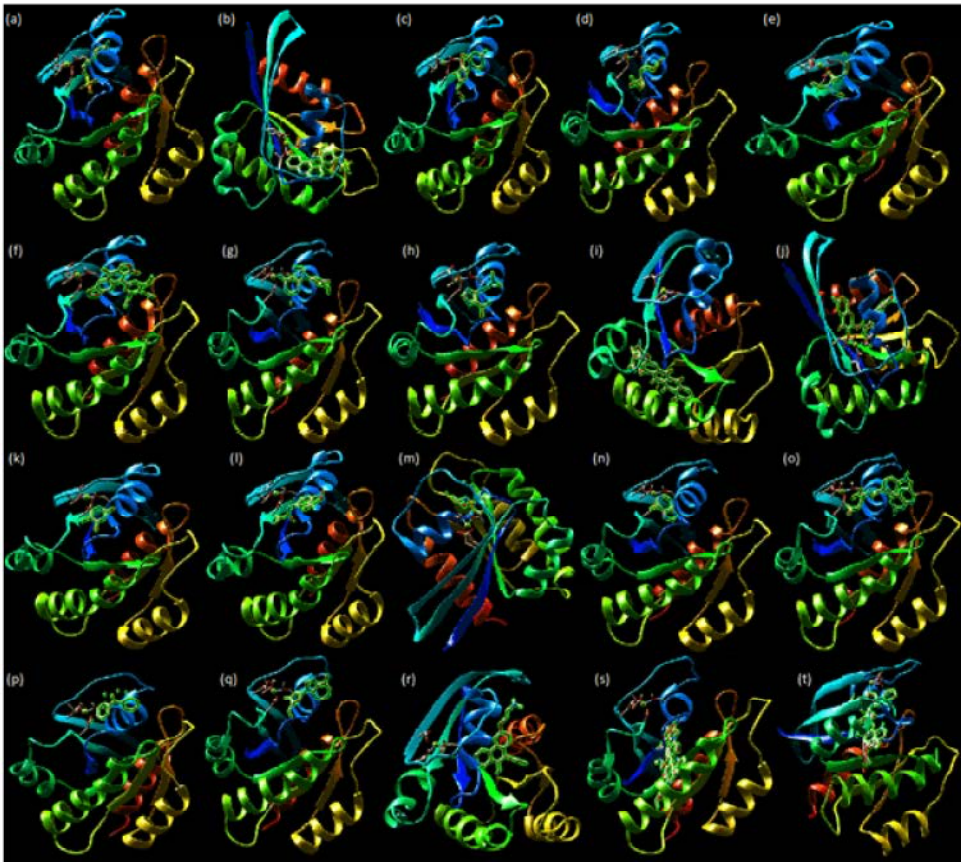

Fig. 2: Different binding site of oncogene protein (PDB I.D-5P21) with different anti-cancer drugs

Figure revealed that residues of oncogene protein (PDB I.D-5P21) cladribine complex were less fluctuates. Side-chains show some fluctuations at different position of RMSF plot at residue numbers 28, 30, 70, 78, 98, 110 and170 in the side chains of the oncogene-cladribine complex. All the other does not shows the major variation in RMSF values and complex will be stable during the RMSF plot.

This Figure ravels that before molecular dynamics simulation THR 34 (Residue 11) having polar charge interact with ligand (Cladribine) atom N19 from donor H-bond with distance and angle 1.89875 Å and 135.056, LYS 117 (Residue 13)interact with ligand atom O29 from H-bond to side chain with distance and angle 2.3919 Å and 112.371, ANS 116 (Residue 12) interact with ligand atom O32 from H-bond to side chain with distance and angle 1.9413 Å and 129.119 and GLY 15 (Residue 2) interact with ligand atom N17 from donor H-bond with distance and angle 2.10856 Å and 97.1047 respectively.

After molecular dynamics several other interaction with different binding sites of ligand can be observed, GLY A-13 (Residue 2) interact with ligand (Cladribine) atom C37 from acceptor H-bond to backbone with distance 1.86459 Å, acceptor angle 166.811 and donor

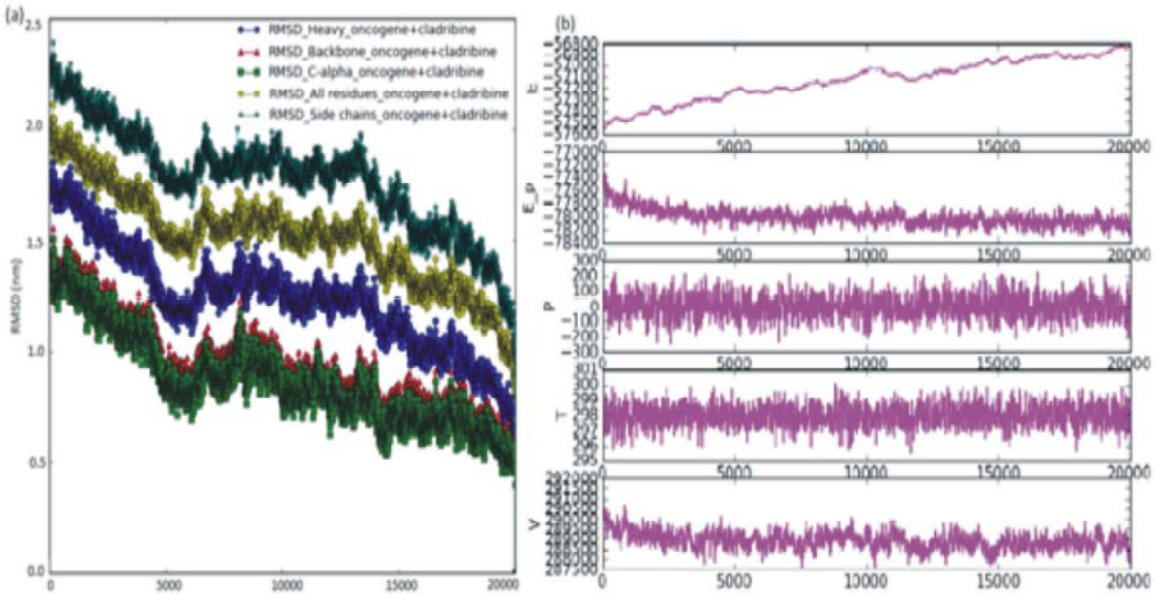

Fig. 3: (a)Plot of root mean square deviation (RMSD) of backbone were calculated using the initial structure as templates. The trajectories were captured every 0.5 ps until the simulation time reaches 20000 ns (5000 ps for oncogene-cladribine complex), (b) energy profile during 20000 ps MD simulation (5000 ps for oncogene-cladribine complex)

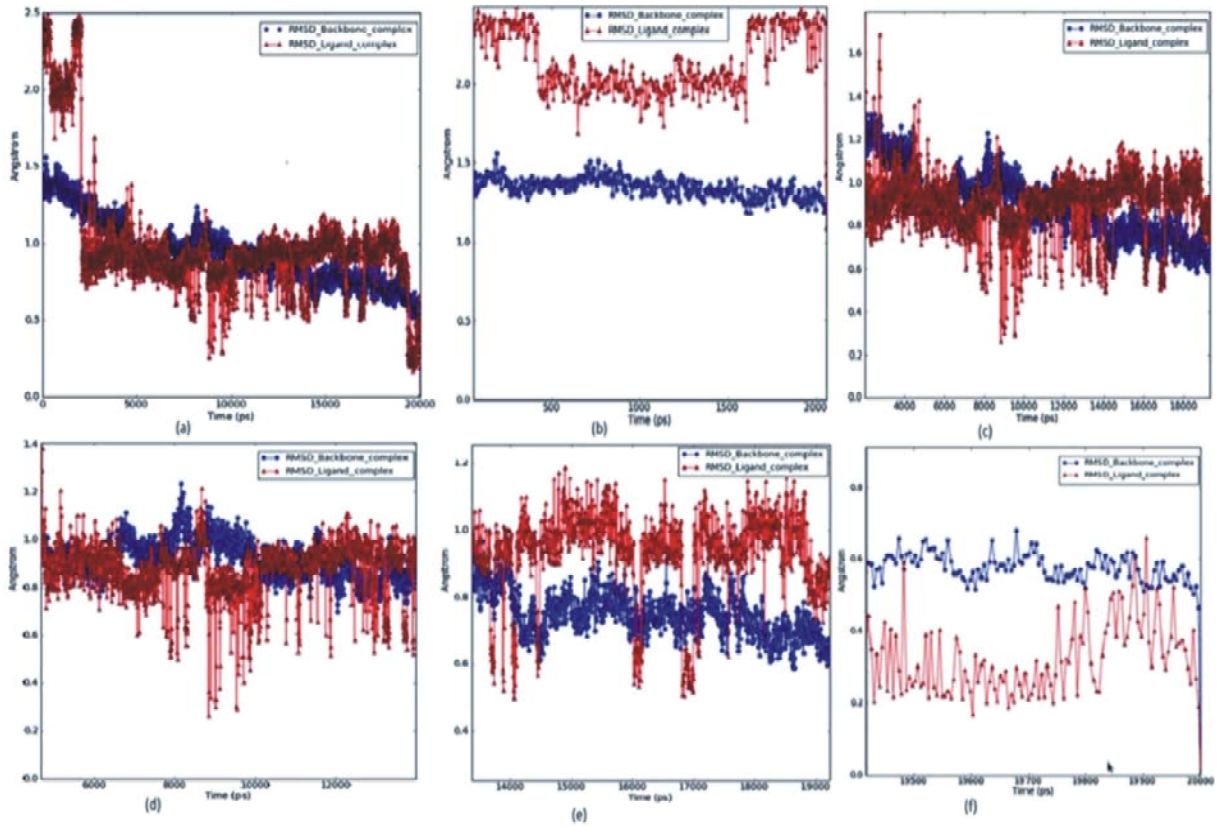

Fig. 4: Root mean square deviation (RMSD) and backbone atom at 2o nanoseconds (ns), different figure shows interaction between ligand-backboneatom coplex at different interval

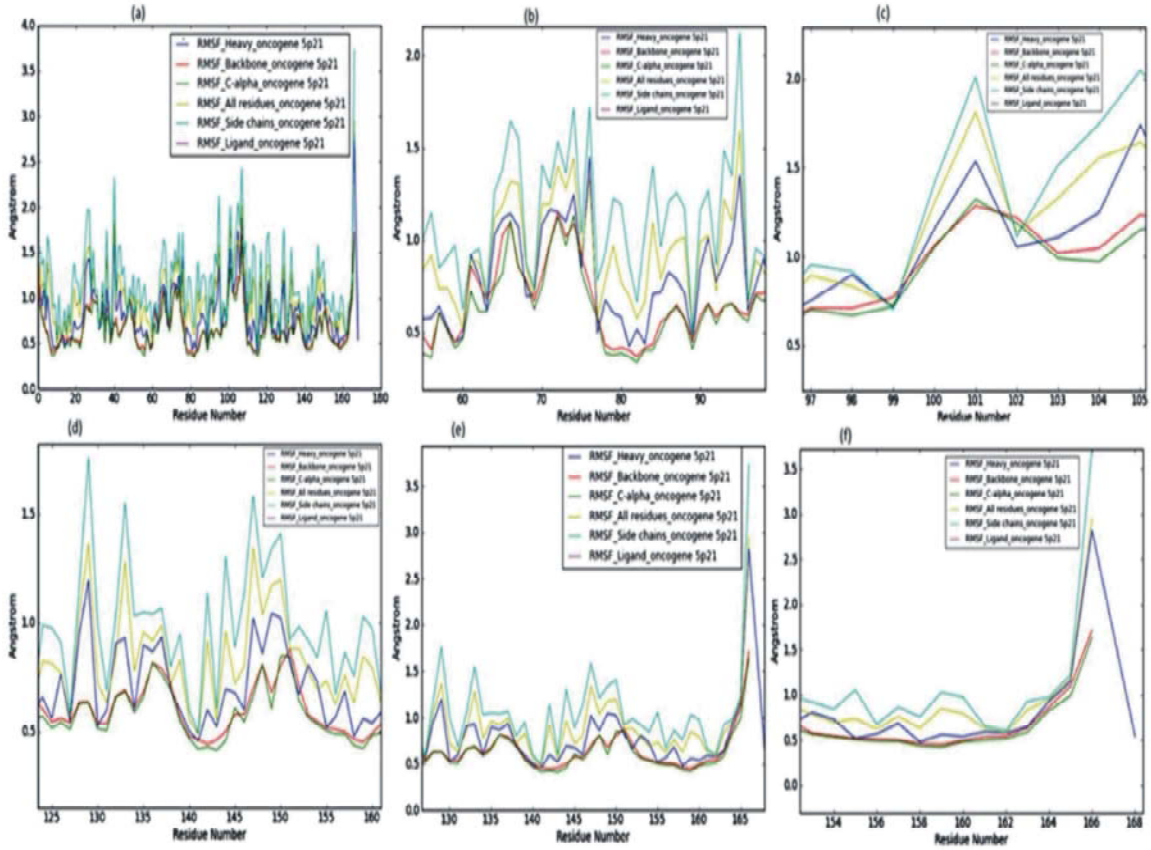

Fig. 5: Root mean square fluctuation (RMSF) of residue during 20000 ps MD simulation [oncogene (PDB I.D-5P21) cladribine complex]

angle 129.13, GLY A-15 (Residue 4) interact with ligand atom N25 from h-bond to backbone distance 2.16365 Å and donor angle 107.252, ASP A-33 (Residue 13) interact with ligand atom N24 from H-bond to side chain with distance 1.74838 Å, acceptor angle 160.936 and donor angle 147.506, LYS A117 (Residue 20) interact with ligand atom O40 from H-bond to side chain with distance 1.83885 Å and donor angle 120.613, VAL A20 (Residue 9) interact with ligand atom O40 from H-bond to backbone with distance 1.97233 Å, acceptor angle 149.723 and donor angle 156.754 respectively.

RMSD Calculation: The Root Mean Square Deviation (RMSD) is used to measure the average change in displacement of a selection of atoms for a particular frame with respect to a reference frame. It is calculated for all frames in the trajectory. The RMSD for frame *x* is:

$$RMSD_x = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(r_i'(t_x)) - r_i(t_{ref}))^2}$$

where *N* is the number of atoms in the atom selection; *tref* is the reference time, (Typically the first frame is used as the reference and it is regarded as time *t*=0); and *r′* is the position of the selected atoms in frame *x* after superimposing on the reference frame, where frame *x* is recorded at time *tx*. The procedure is repeated for every frame in the simulation trajectory.

Protein RMSD: The above plot shows the RMSD evolution of a protein (Left *Y*-axis). All protein frames are first aligned on the reference frame backbone and then the RMSD is calculated based on the atom selection. Monitoring the RMSD of the protein can give insights into its structural conformation throughout the simulation. RMSD analysis can indicate if the simulation has equilibrated — its fluctuations towards the end of the simulation are around some thermal average structure. Changes of the order of 1-3 Å are perfectly acceptable for small, globular proteins. Changes much larger than that, however, indicate that the protein is undergoing a large

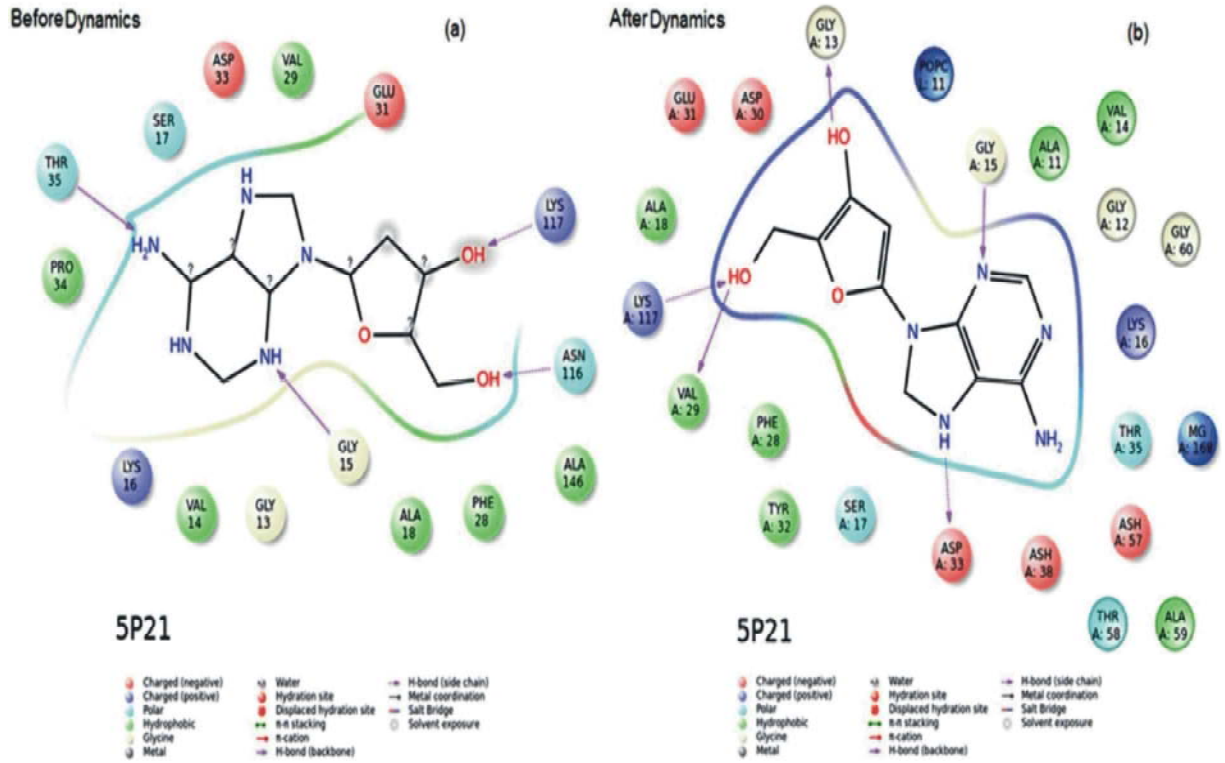

Fig. 6: Interaction of Drug (cladribine) with amino of oncogene protein (PDB l.D-5P21) before and after molecular dynamics

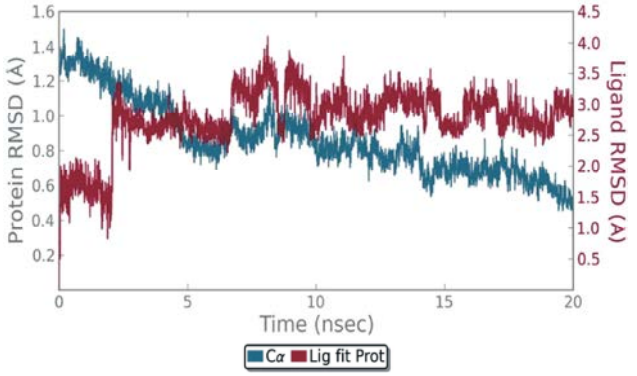

Fig. 7: RMSD of protein and ligand interaction

conformational change during the simulation. It is also important that your simulation converges — the RMSD values stabilize around a fixed value. If the RMSD of the protein is still increasing or decreasing on average at the end of the simulation, then your system has not equilibrated and your simulation may not be long enough for rigorous analysis.

Ligand RMSD: Ligand RMSD (Right *Y*-axis) indicates how stable the ligand is with respect to the protein and its binding pocket. In the above plot, 'Lig fit Prot' shows the RMSD of a ligand when the protein-ligand complex is first aligned on the protein backbone of the reference and then the RMSD of the ligand heavy atoms is measured. If the values observed are significantly larger than the RMSD of the protein, then it is likely that the ligand has diffused away from its initial binding site.

CONCLUSION

Virtual screening methods are extensively used in drug discovery process to reduce the time spent on the

research as well as expenditure. The approach utilized in this study resulted in identifying the drugs which have high efficacy of binding site with oncogene protein. In the present study, target protein oncogene of an anticancer chemotherapeutic drugs methotrexate, vincristine, vinblastine, amifostie, amscarine, azacitidine, busulfan, carmustine, podophylotoxin, cladrribine, dacarbazine, doxorubicin, fluorouracil, flutamide, ifosfamide, mercaptopurine, mitotane, pentoatatine, tamoxifine and etopside was used for drug target interaction study. 3D Structure of oncogene was predicted and validated by using bioinformatics tools. Further, modelled 3D structure of oncogene (PDB 5P21) was used to dock selected drugs using a flexible docking method of auto-dock. Result showed that among 20 drugs, cladribine had scored -7.17 binding energy. Thus, oncogene and cladribine were found to be more stable binding interaction with the other anti-cancer drugs. After molecular docking analysis the selected compound which has highest negative energy was further used for molecular dynamics simulation study to predict the interaction of oncogene-cladrabine after and before. This can be shown that of which amino acid residue makes the interaction with cladribine coordinates. This study may be the subject of experimental validation and clinical trial to establish these said analogues as more potent drug for the treatment of different cancers.

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